Contributions of Correlated Motions in Dendritic Catalysis: Stereoselectivity of Asymmetric Direct Aldol Reactions.

A Senior Honors Thesis

Presented in partial fulfillment of the requirements for graduation with distinction in biochemistry in the undergraduate colleges of

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By

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Abstract

Biological macromolecules, such as proteins, maintain a high level of internal organization through non-bonded interactions such as hydrogen bonds, $\pi - \pi$ stacking, and non bonded intermolecular electrostatic forces. However, the ability to control similar synthetic microenvironments has presented considerable difficulty. The globular structure and structural stability of dendrimers places them among the few synthetic macromolecules available which are potentially capable of mimicking biological systems. Many systems have been designed with linkages which are too flexible, thus rendering them incapable of the structural stability exhibited by molecules such as proteins. The specific class of dendrimers investigated here has been shown to exhibit cooperative motions due to structural preorganization and hydrogen bonding interactions. It is the aim of this project to achieve an understanding of the influence of correlated dynamic motions on the selectivity of a chemical process within a microenvironment. These correlated motions have been shown to increase the helical bias of dendritic secondary structure, and current research has shown that these correlated motions contribute to the amplification of the stereoselectivity of a catalytic process as well. Research on this project is underway to determine the scope of this reaction in terms of substrate specificity and stereoselectivity.

Introduction

Proteins and other biological macromolecules rely heavily on extensive long range interactions to maintain a high level of internal organization, communication between distant atoms, and help to coordinate movements within the protein as a whole.[1] The enhanced cooperativity and structural stability observed in proteins can thus be accounted for by the coupling of secondary and tertiary structures through interactions such as hydrogen bonding, π–π stacking and solvophobic effects.[2] Thus, the structure and function of proteins is an inherently cooperative feature.

These types of correlated motions are abundant in nature.[3] The structural changes which take place in hemoglobin upon oxidation of the iron atom of the heme group are a well studied example. Hemoglobin consists of four subunits: two α and two β, each of which contains a prosthetic heme group (an iron containing porphyrin). In its deoxy (T) state, the iron (II) molecule lies slightly out of the plane of the porphyrin group by approximately 0.6Å, and is penta coordinated to the four nitrogen atoms of the porphyrin ring, and the nitrogen of a histidine residue within the protein.

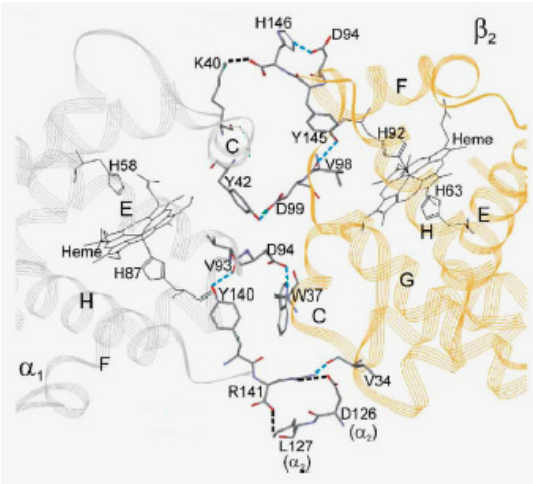


Figure 1. $\alpha_1\beta_1$ subunit of hemoglobin. The iron of the heme group is bound to the four nitrogens of the porphyrin ring, and a histidine residue within the protein (residues H87 and H92). Upon oxidation, the bonds to the iron shorten, moving it into the plane of the porphyrin ring, and shifting the corresponding histidine residue, and the α helix which it lies in (F). Thus, an overall shift in the tertiary structure of the subunit is observed.[4]

Upon oxidation of the iron (II) to iron (III), the iron-nitrogen bonds within the heme group shorten by approximately 0.1 Å, thus pulling the iron molecule and the attached histidine residue closer to the plane of the porphyrin ring. The alpha helix within which the histidine residue lies is also pulled closer to the porphyrin ring, and an overall shift in the tertiary structure of the subunit is observed.[4] Furthermore, due to the communication between subunits, an allosteric effect is observed. It is preferential for all subunits to bind oxygen and shift their structures at the same time, rather than for one subunit at a time to bind oxygen and shift its structure.

Correlated motions help not only to coordinate movements within the protein as a whole, as in hemoglobin, but small internal motions have been shown to increase the overall stability of the protein secondary structure, as was shown with Streptococcal protein G.[5] In comparing a series of β-sheet mutants of the B1 domain of Streptococcal protein G, a positive correlation was observed between increased backbone flexibility and the thermal stability of the protein.[6] It would seem that such motions would disturb the secondary and tertiary structure of the protein by disrupting non covalent interactions, such as hydrogen bonding and π–π stacking, however, these increased internal motions were not shown to be large enough to have such an effect. One hypothesis is that these small internal movements may improve the thermal stability of the protein by contributing to the heat capacity of unfolding.

In the structure of yeast phosphoglycerate kinase, correlated motions aid in catalysis.[3] Phosphoglycerate kinase is involved in the cleavage and transfer of a phosphate group from 1,3-bisphosphoglycerate (1,3-BPG) to a molecule of adenosinediphosphate (ADP) to generate adenosinetriphosphate (ATP) and 3-phosphoglycerate (3PG) in glycolysis.[1] Initially, upon binding both substrates, the protein remains in an open structure, with the bound ADP and 1,3-BPG separated by about 12Å.[7] This is too far apart for a catalytic transfer of the phosphate group to take place, and a rotation of the two domains by 10-20 ^{o} takes place to bring the substrates together in a water free environment (Figure 2).

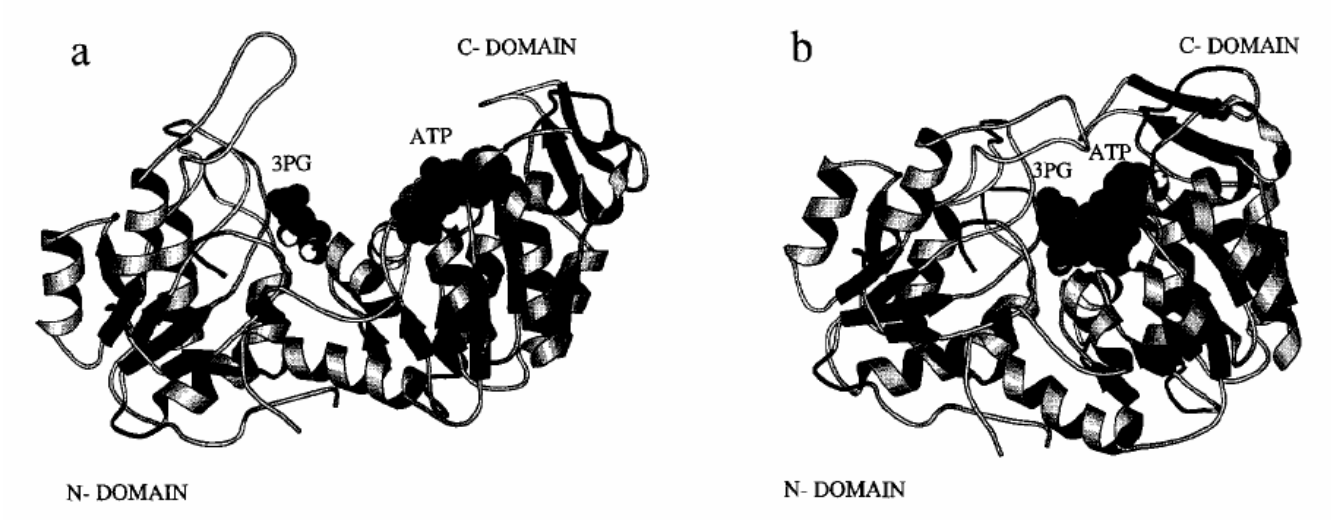


Figure 2. Open (a) and closed (b) forms of yeast phosphoglycerate kinase, showing the position of the substrates (ATP and 3PG) relative to one another after and during catalysis.[7]

Examples such as these demonstrate that synchronized motions undoubtedly play an important role in the efficiency, stability and catalytic activity of biological molecules. The ability to mimic such motions provides opportunity to gain insight into how they specifically contribute to these and other types of systems. Dendrimers provide an easily accessible synthetic route to creating synthetic systems that exhibit these same types of correlated motions. The study of such systems provides an opportunity to achieve an understanding of the influence of correlated dynamic motions on the selectivity of a chemical process within a microenvironment. These correlated motions have been shown to increase the helical bias of macromolecular secondary structure, such as in a polyisocyanate system.[5] These polymers exhibit a stiff helical structure due to steric repulsion between adjacent carbonyl groups along the chain. As achiral molecules, these polymers exist with equal amounts of left and right handed helical segments. However, upon introduction of a small number of chiral, nonracemic monomers into the chain, the small forces between the monomer units combine to become one large force, and an excess of one helical sense is seen.[8] Current research provides evidence that these correlated motions also contribute to amplification of the stereoselectivities of a catalytic process. Furthermore, by learning what does and does not contribute to a successfully stable and coordinated supermolecular synthetic structure, perhaps

we can elucidate which features of biological macromolecules contribute to and play an important role in this same function.

Dendrimer Chemistry

The study of dendrimers is one of the more recent fields to develop in chemistry today, including dendritic catalysis. Dendrimers are a class of macromolecules which have highly branched, complex, and ordered structures.[9] These highly ordered structures and substructures place them among the few synthetic macromolecules available which mimic biological systems in their complexity and order.[10] It is the inherent nature of the complexity of dendrimers that allows room for substantial structural modifications to alter various properties such as size, shape, folding, stability, and rigidity. Thus, with the capacity to control dendritic structure, dendritic catalysts can be engineered specifically for a given type of reaction by varying factors such as size, flexibility and folding to provide an optimal microenvironment for catalytic activity. [11]

The lack of organization in other reported dendrimers indicates that developing a suitable dendrimer whose structure is both stable and functional depends on several factors. Ideally, a dendrimer designed for catalysis needs to possess some degree of structural adaptability to be able to accommodate substrates without losing structural integrity. In order to accomplish this both the covalent structure and non-covalent interactions must be taken into account. Firstly, the dendrimer must be organized in such a way that the subunits pack in an efficient and coordinated manner. In the systems designed by the Parquette group, the degree and type of dendrimer compaction has been shown to strengthen or weaken secondary structure, with the more coordinated and compact dendrimers exhibiting a higher degree of stability than those that were compacted to a lesser degree and in a more random, uncoordinated manner. With the dendrimers to be examined in this study, the higher degree of compaction serves to stabilize secondary structure via the development of a helical order. [10] However, structural compaction alone is not enough. Various non-bonded interactions (hydrogen bonding, Van der Waals interactions) are

necessary to stabilize the network of subunits.[12] In this dendritic system, these non-covalent interactions have been combined to couple the movements of several subunits, thus increasing the energetic difference relating one conformational state to another. This conformational energy gap, when combined with steric repulsions, in turn causes all of the dendritic subunits to adopt the same conformation, thereby inducing conformational cooperativity and stability within secondary structure.[10,11]

In order to develop a suitable dendritic catalyst, not only is a stable dendrimer backbone necessary, but one must consider where to place the catalytic sites. Coordination of the catalyst and substrate as well as chemical and structural changes that occur with the progression of the reaction must both be considered.

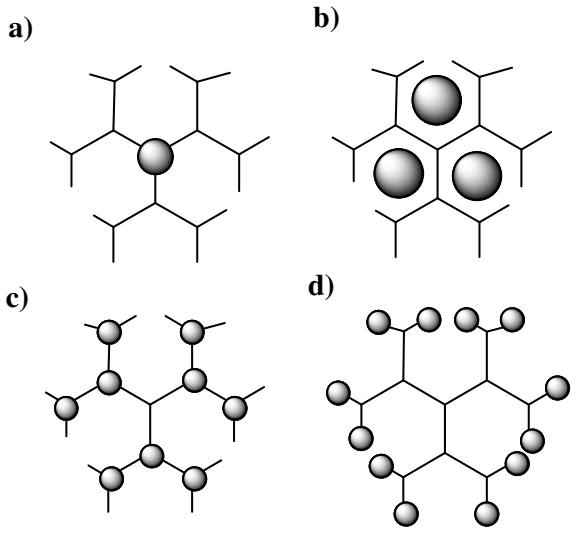


Figure 3. Different models of dendritic catalysts, with catalytic centers located at the core (a), in pockets (b), on the branches (c), or at the periphery (d).

There are several varying models for dendritic catalysts, most of which fall into a few categories: catalytic sites may be located at the core of the dendrimer (a), in pockets within the dendrimer (b), on the branches of the dendrimer (c), or at the periphery (d). (Figure. 3) Catalyst design and placement varies from system to system. Metals can be most easily placed within pockets, or at the center of the dendrimer where they can coordinate to corresponding ligands, while smaller organocatalysts are more easily placed at the periphery of the dendrimer, so that they can directly coordinate and complex with a given substrate.[11]

Previous approaches to designing a dendritic catalyst have taken advantage of such effects as pre-concentration of catalytic sites (the "dendrimer effect", an increase in effective turnover rate due to increased catalytic site concentration at higher generations), or creation of an inner environment which functions to stabilize key reaction intermediates, or shield functional groups at the dendritic core.[13] Dendrimers designed by Francavallia (Figure 4) with terminal selenium moities (4) were shown to catalyze the oxidation of bromine, which was captured with cyclohexene (5). [13,14] A cooperativity, attributed to the proximity of the adjacent phenylseleno groups, was observed that enhanced the catalytic rate beyond what would be observed due to concentration alone.

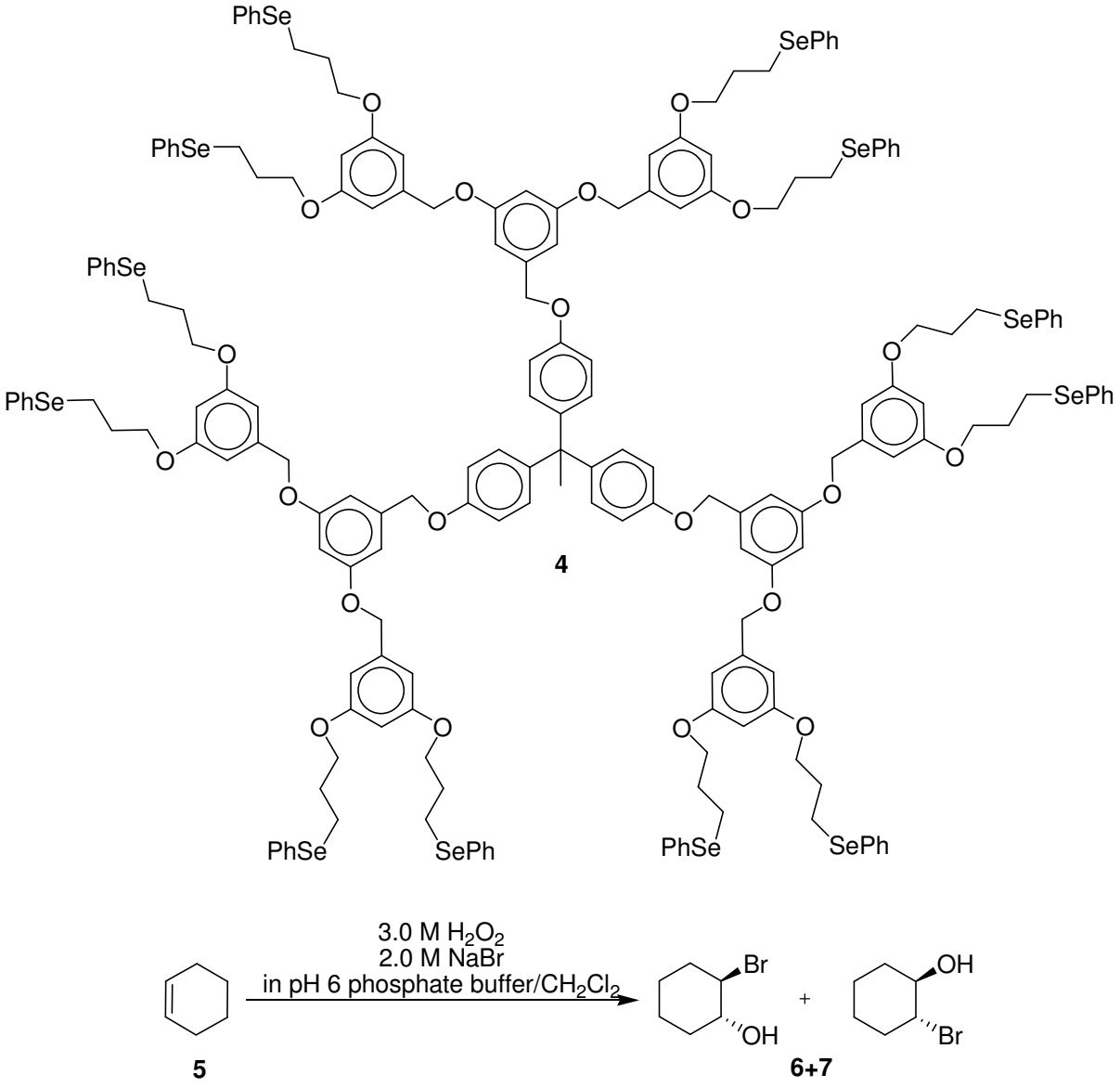
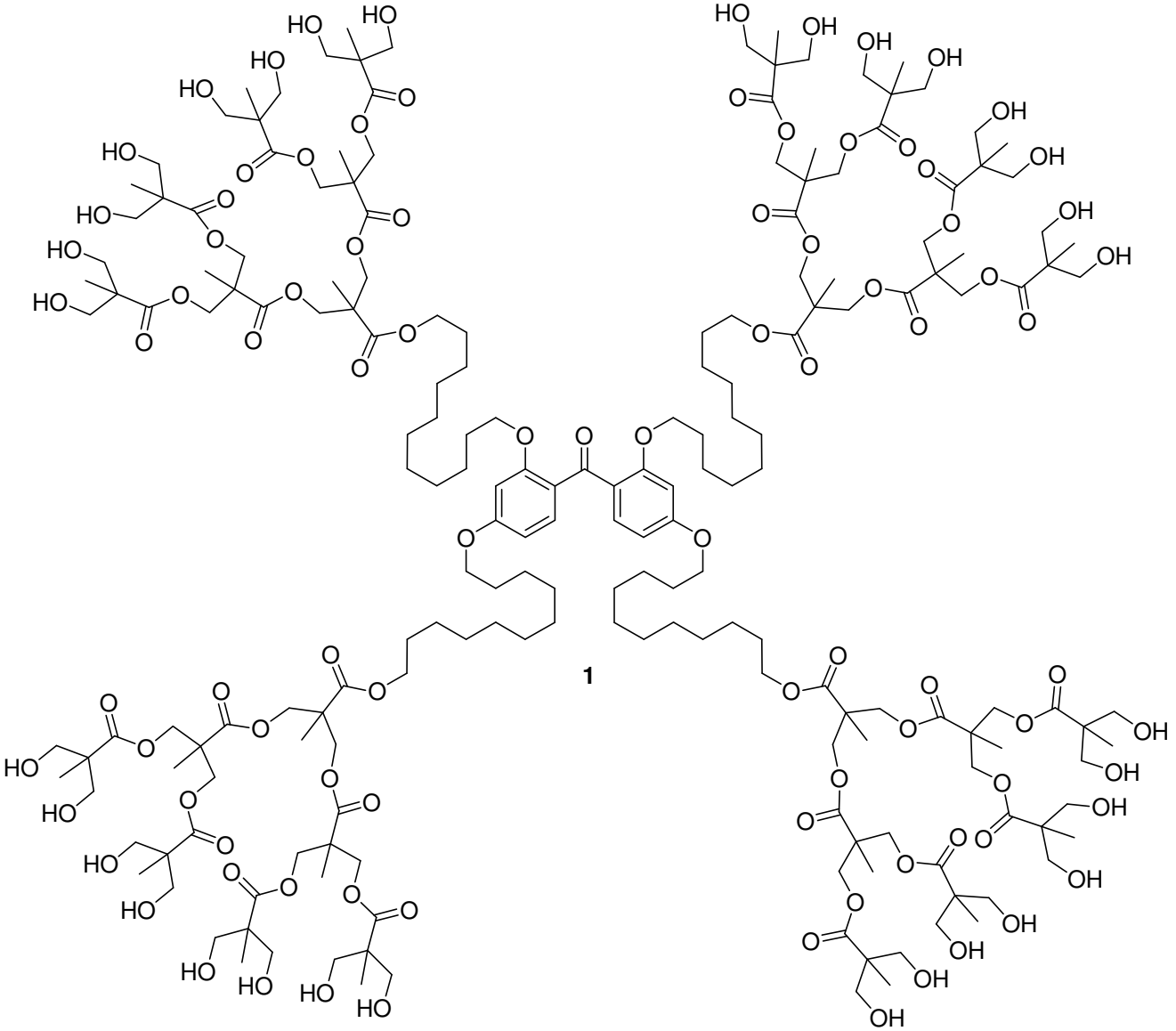


Figure 4. Poly (benzyl ether) dendrimer with terminal selenium moities.

Another example of previous work in dendritic catalysis is work done by Frechet and co-workers (Figure 5). The catalyst designed by Frechet (1) was shown to promote a 4+2 cycloaddition reaction of singlet oxygen to cyclopentadiene (2) in methanol.[15,16] The cyclopentadiene was bound in the more favorable hydrophobic interior of the dendrimer to react with the singlet oxygen generated by the benzophenone core. The more polar cyclocyloaddition product (3) was more stable outside the dendritic microenvironment, and subsequently reduced with thiourea to generate (4).



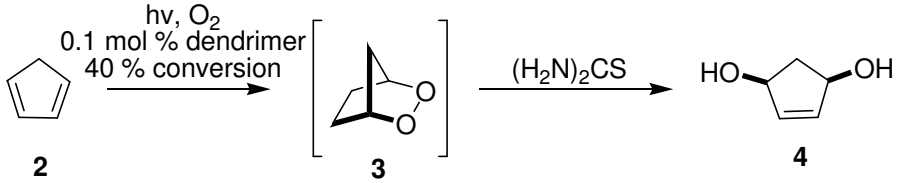


Figure 5. light driven dendrimer designed by Frechet.

Poly(amidoamine), PAMAM, dendrimers are also good mimics of globular protein structures. In work done by Liu and Breslow, PAMAM dendrimers were synthesized and used in catalysis of transamination reactions (Figure 6). Pseudo-first-order kinetics and saturation effects which followed Michaelis-Menten kinetics were observed.[17]

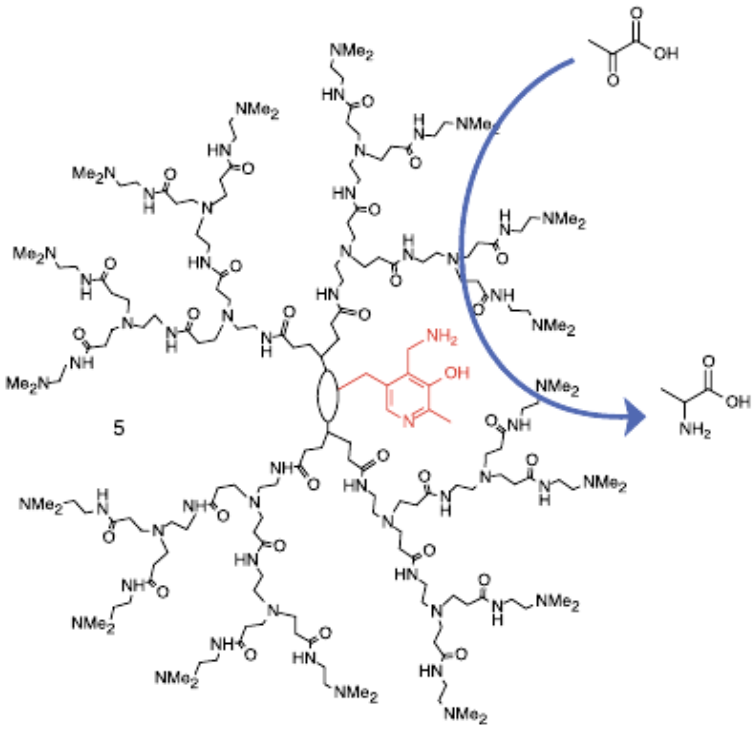


Figure 6. PAMAM dendrimer used in transamination reactions by Liu and Breslow.

Current research employs a pyridine-2,6-dicarboxamide branching unit in order to utilize intramolecular interactions such as hydrogen bonding and π–π stacking to stabilize the dendritic framework. With a basic understanding of the principles behind dendrimer structure and design, this project seeks to explore how these concepts extend into the field of catalytic chemistry, with the main focus being on how these networked, coordinated dendrimer structures affect catalytic rate. It is hoped that the coordinated cooperativity of these dendrimers can be harnessed and utilized to control the selectivity of a reaction, and that the role of dendrimers as synthetic catalytic supports can be expanded. By engineering dendrimers with a chiral secondary structure, we can create a coordinated cooperativity within the dendrimer that will extend to the catalytic sites, thus increasing the enantioselectivity and specificity of a reaction. Factors such as reaction rate and yield will be examined and compared both

between subsequent generations of dendrimers and with non-dendrimeric systems in order to assess this relationship between dendritic structure and function.

Methodology

The ability to design a suitable and stable dendrimer skeleton has proven to be one of the more difficult tasks in engineering a dendritic catalyst. The dendrimer itself must be rigid enough to maintain its internal organization, yet flexible enough to coordinate a reaction. A structure which is too flexible may collapse on itself, while one which is too rigid will not be mobile enough to properly coordinate to its substrate. However, by developing a dendritic structure based on pyridine-2,6-dicarboxamide, these issues can be circumvented. (Figure 7)

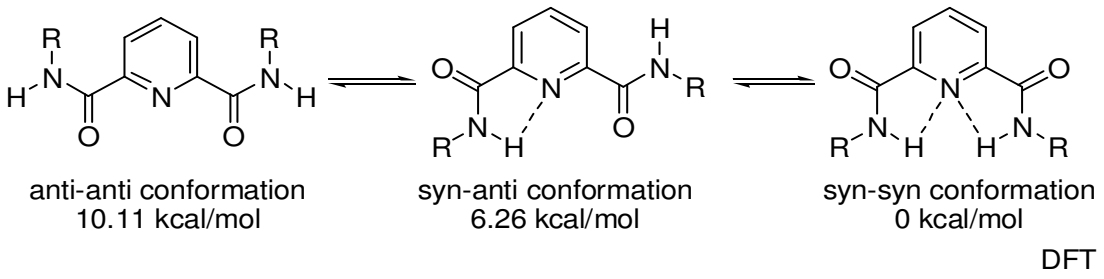


Figure 7. Anti-anti, syn-anti, and syn-syn conformations of pyridine-2,6-dicarboxamide along with the corresponding energies as calculated by DFT. The syn-syn conformation is of the lowest energy as it is stabilized by both Hydrogen bonds and a more favorable dipole moment.[18]

The chemical structure of pyridine-2,6-dicarboxamide is useful for several reasons: a stabilized internal dendritic framework is created, and a local chirality is induced, thus resulting in conformational cooperativity between the dendron branches, a feature which is unique to this class of dendrimers. The *syn-syn* conformation in pyridine-2,6-dicarboxamide is stabilized by hydrogen bonding between the amide hydrogens and the pyridine nitrogen, as well as through creation of a more favorable dipole moment.[18] Furthermore, due to steric repulsions between the R groups on the amide nitrogens, these groups are forced to lie above and below the plane of the pyridine ring. (Figure 8)

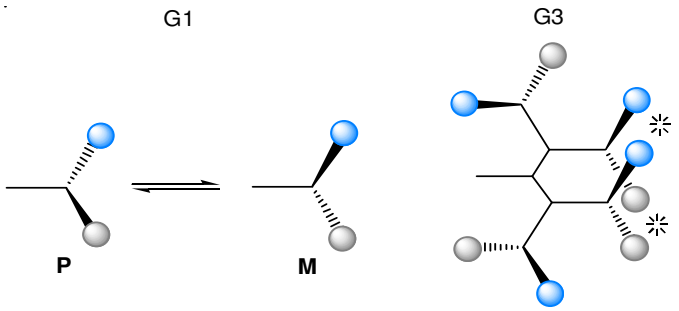


Figure 8. Induction of helical bias with larger dendrimer generations due to steric repulsions and increased packing efficency.

This gives the molecule a helical chirality (*M* or *P*). With smaller R groups, the molecule is easily able to convert between *M* and *P* helices, however as bulkier R groups are added, the energy difference in switching between various conformations of pyridine-2,6-dicarboxamide is amplified, and the molecule becomes less likely to interconvert. Steric repulsions at the periphery of the dendrimer further amplify this energetic gap, and cause branches to adopt the same conformation to minimize such repulsions, thus resulting in conformational cooperativity and overall helical conformation within the secondary structure. [12,19] By adding an anthranilamide turn unit, or a chiral molecule to the amine functionalities of the branching unit, this conformational cooperativity can be utilized to give the dendrimer an overall helical preference (*M* or *P*). The helical preference in the secondary dendrimer scaffold should also induce a higher order of selectivity in catalytic systems, an effect which should increase with subsequent dendrimer generations, as the energy gap between conformational states increases, thus producing a better, more enantioselective catalyst. Overall, the pyridine-2,6-dicarboxamide based structure provides for a dendrimer which is both stable and rigid, yet has a substantial amount of flexibility as well – a useful characteristic in catalytic (and biological) systems.

Previous Work

A. Preston and B. Saha previously used these sorts of dendritic systems in yttrium catalyzed epoxide openings (Figure 9). Upon increasing the generation of the dendrimeric catalyst, a corresponding increase in enantioselectivity was observed. Furthermore, as the dendritic structure became more compact (a turn unit was added to construct a type II dendron), the enantioselectivity of the reaction was

further increased.

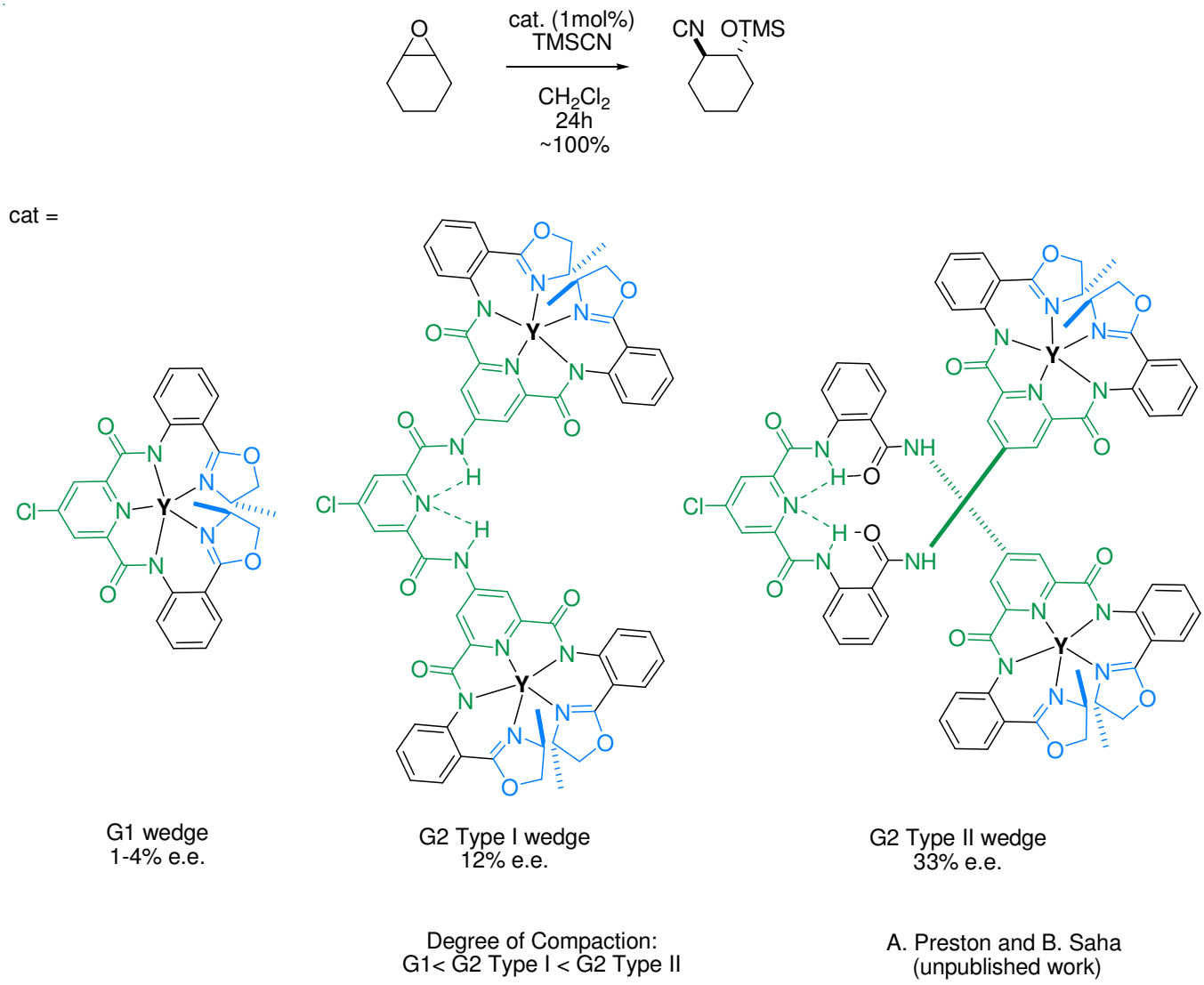
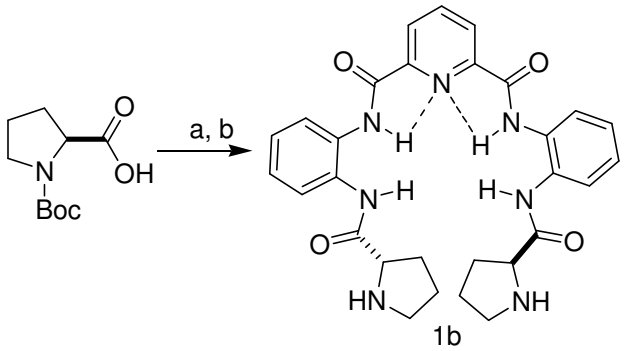


Figure 9. Previous work by A. Preston and B. Saha indicates that increased correlated motions produce a corresponding increase in the enantioselectivity of asymmetric epoxide openings.

These results indicate that the orchestrated motions within pyridine-2,6-dicarboxaimide type dendrimers do play an important role in the stereoselectivity of a reaction. However, the yttrium systems were difficult to work with and little was known about them mechanistically. The use of an organocatalytic system, such as L-prolinamide, simplifies procedures and has a well known reaction mechanism. Additionally, L-prolinamide is biomimetic in its reaction mechanism, and is often preferred over similar metallic systems because it is more environmentally friendly and less prone to contamination.

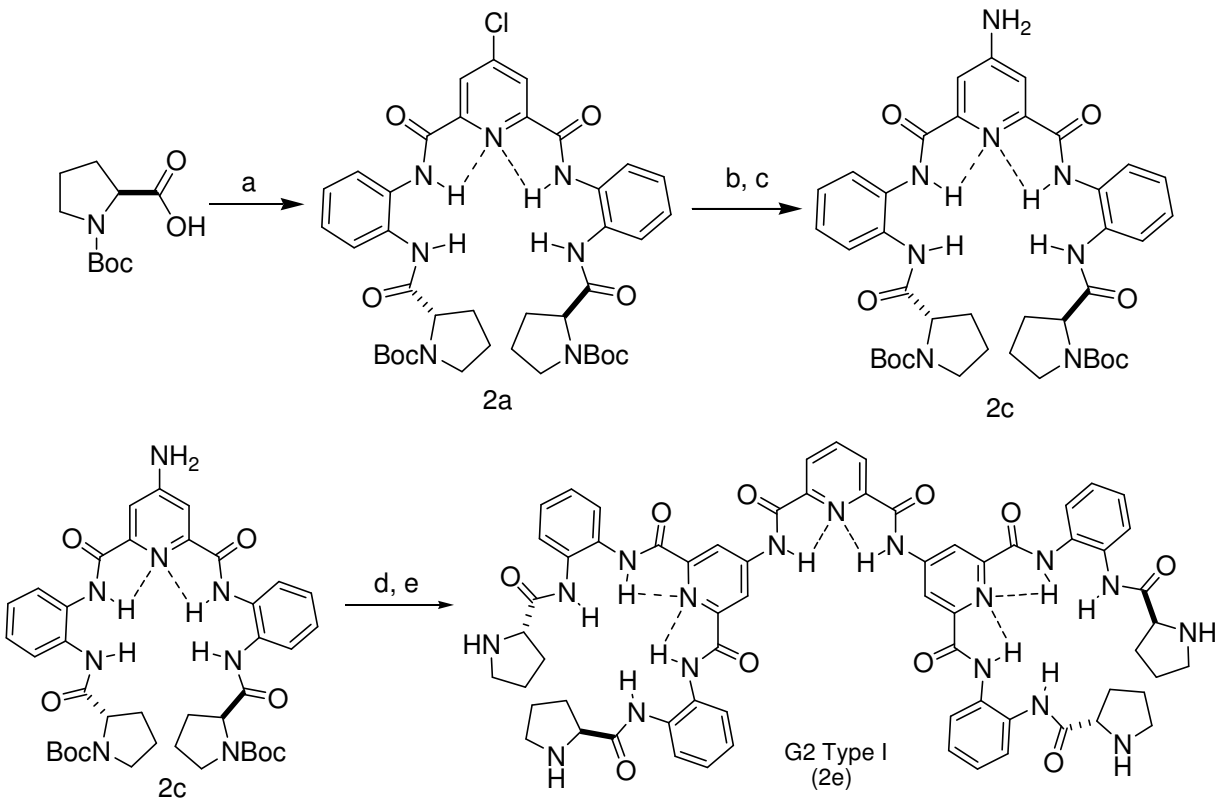
Synthesis



a: 1) Ethyl Chloroformate, THF, Et_3N, 0°C to r.t., 2h
2) o-Phenylene diamine, r.t., 1h.
3)Pyridine-2,6-dicarbonyl dichloride, Et_3N, 0°C to r.t., 12h (51-80%)
b:TFA, anisole, CH_2Cl_2, 4-6h (99%)

Scheme 1. Synthesis of G1 dendron.

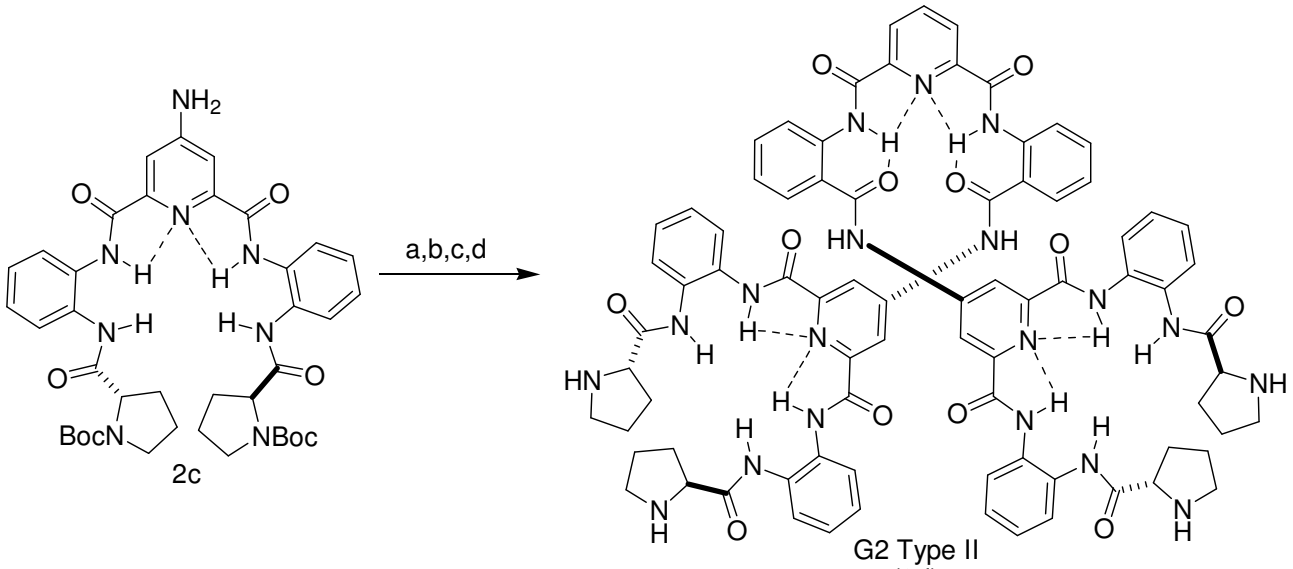
It is the aim of this project to achieve an understanding of the influence of correlated dynamic motions on the selectivity of a chemical process within a microenvironment. The dendrimer scaffolding is constructed from a repeated dendron wedge, which can either be used directly as a first generation catalyst, or coupled to additional branching units to form larger generational wedges. The first generation dendron wedge is synthesized utilizing an all in one pot reaction (Scheme 1). First, the amine of L-proline is protected through a reaction with boc anhydride to form the boc protected L -proline derivative. Then, the protected L -proline is reacted with ethyl chloroformate to form the anhydride, which is coupled *in situ* with one equivalent of phenylne diamine, followed by a half equivalent of pyridine-2,6-dicarbamoyl chloride to generate the boc protected first generation wedge. To synthesize the second generation wedges, the same initial reaction of boc protected proline with ethyl chloroformate, followed by one equivalent of phenylene diamine is run. However, in the third step of the reaction, the pyridine-2,6-dicarbamoyl chloride is replaced with a half equivalent of 4-chloropyridine-2,6-dicarbamoyl chloride to generate the first generation wedge with a chlorine at the focal point. Next, the focal point of the G-1 wedge is manipulated through an azide displacement and palladium on carbon hydrogenation to form a primary amine.



a: 1) ethyl chloroformate, THF, Et_3N, 0°C to r.t., 2h 2) *o*-phenylene diamine, r.t., 1h. 3) 4-chloro-pyridine-2,6-dicarbonyl dichloride, Et_3N, 0°C to r.t., 12h (51-80%).
b: NaN_3, DMF 60-70 °C, 44 h. (41-99%)
c: Pd/C, H_2 EtOAc, r.t., 12h. (40-84%)
d: pyridine-2,6-dicarbonyl dichloride, Et_3N, DMAP, CH_2Cl_2, 0°C to r.t. (84-85%)
e: TFA, anisole, CH_2Cl_2, 4-6h (50-96%)

Scheme 2. Synthesis of G2 type I dendron.

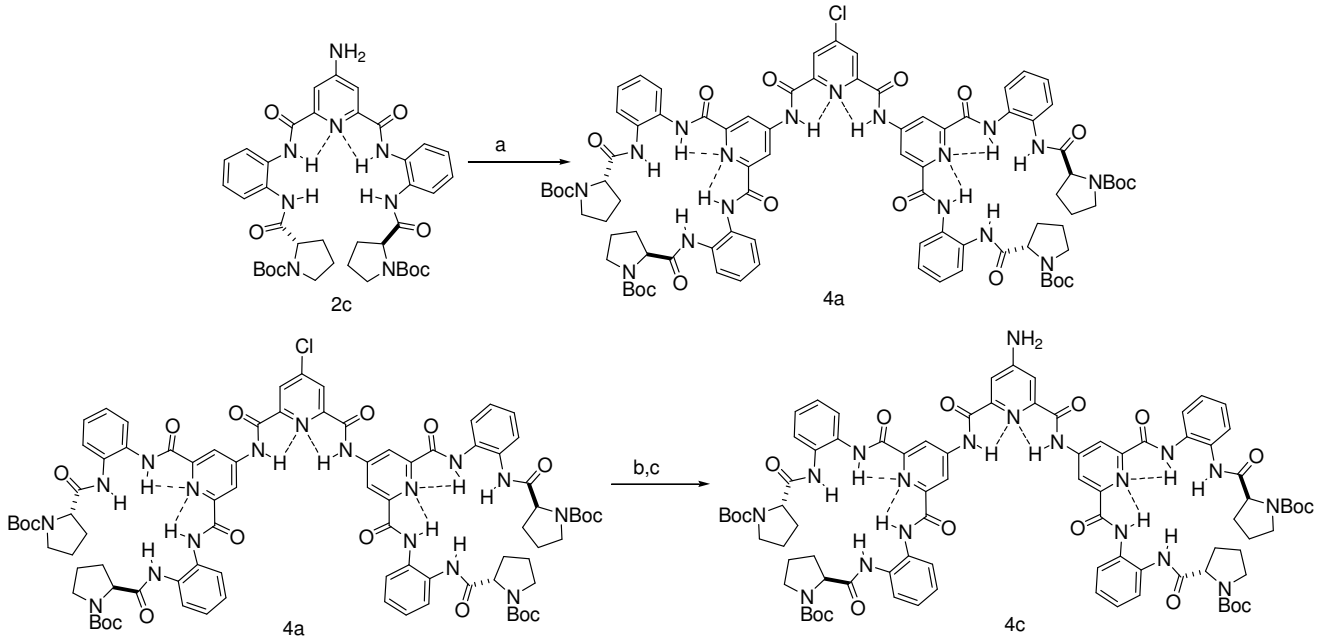
Larger generations can then be generated through coupling of the primary amine at the dendron focal point to pyridine-2,6-dicarbamoyl chloride (Scheme 2). Furthermore, a variation of the G-2 dendrimer wedge (Scheme 3) can be generated by coupling the G-1 wedge to *o*-nitro benzoyl chloride, performing a palladium on carbon hydrogenation, and then coupling the resulting wedge to pyridine-2,6-dicarbamoyl chloride to form a second variant of the G-2 wedge (G-2 type II). It is hypothesized that the addition of the *ortho* turn unit should increase packing efficency in these dendrimers and lead to increased conformational cooperativity.



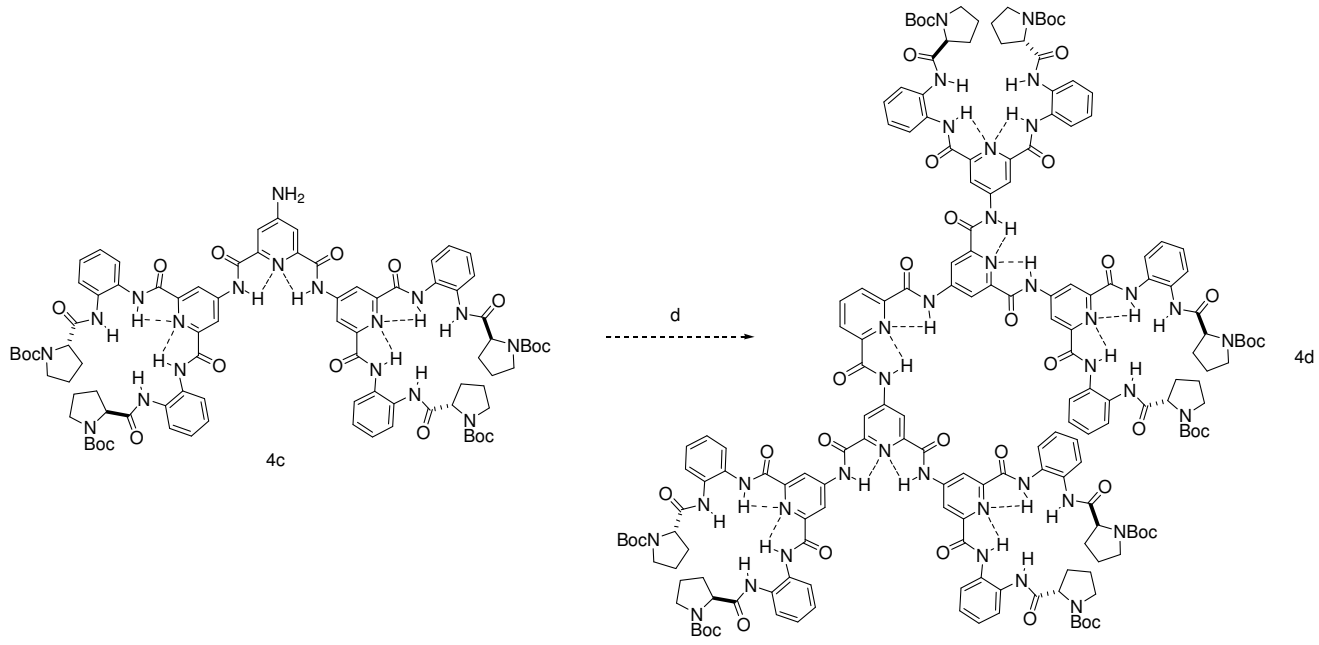
a: 2-nitrobenzoic acid chloride, pyridine, CH_2Cl_2, 0°C to r.t. (48-84%)
b: Pd/C, H_2 EtOAc, r.t., 12h. (40-84%)
c: pyridine-2,6-dicarbonyl dichloride, Et_3N, DMAP, CH_2Cl_2, 0°C to r.t. (84-85%)
d: TFA, anisole, CH_2Cl_2, 4-6h (50-96%)

Scheme 3. Synthesis of G2 type II dendron.

Furthermore, syntheisis of a G3 dendron is currently underway. First, the G1 dendron was coupled to 4-chloro pyridine-2,6-dicarboxylic acid chloride, followed by an azide displacement and hydrogenation to yield the G2 type I dendron with an amine at the focal point. The modified G2 dendron will then be coupled to pyridine-2,6-dicarboxylic acid chloride to give the boc protected G3 type I dendron, and subsequently deprotected using trifluoroacetic acid and phenol. (Scheme 4).



a: 1) ethyl chloroformate, THF, Et_3N, 0°C to r.t., 2h 2) *o*-phenylene diamine, r.t., 1h. 3) 4-chloro-pyridine-2,6-dicarbonyl dichloride, Et_3N, 0°C to r.t., 12h
b: NaN_3, DMF 60-70 °C, 44 h.
c: Pd/C, H_2 EtOAc, r.t., 12h.



d: Pyridine-2,6-dicarbonyl dichloride, Et_3N, DMAP, CH_2Cl_2, 0°C to r.t.

Scheme 4. Synthesis of G3 Type I dendron

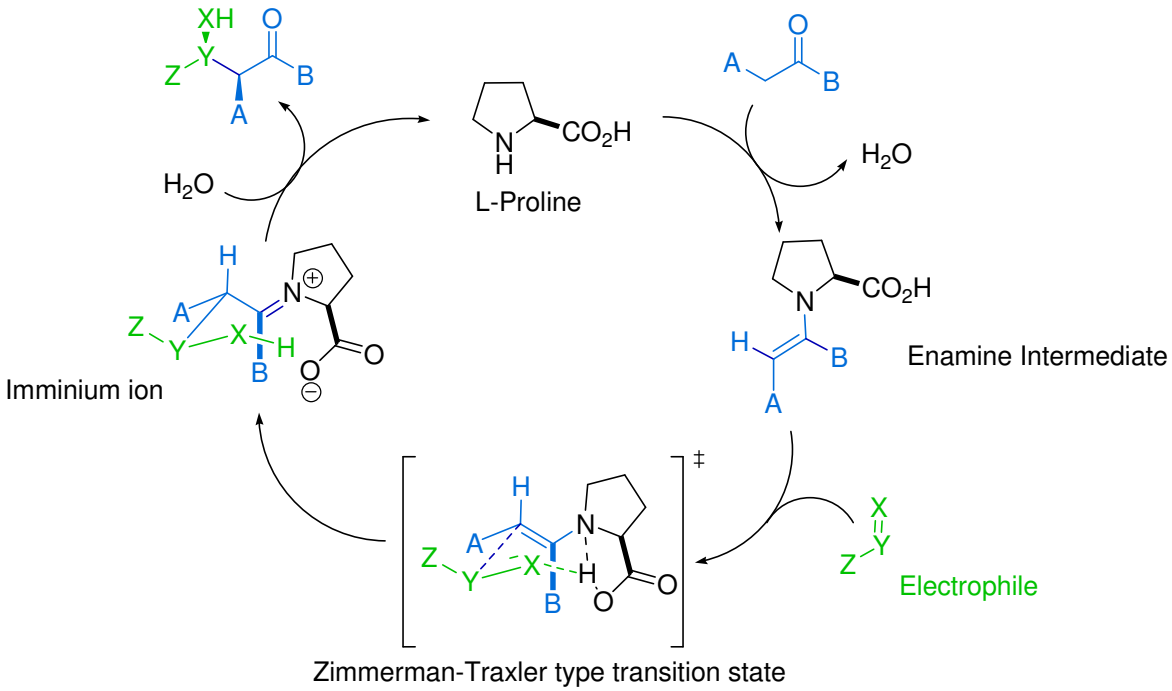


Figure 10. Proposed catalytic mechanism of L-proline.

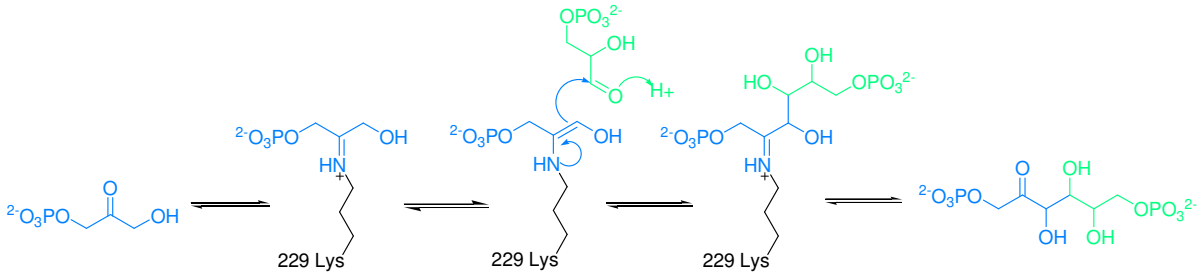


Figure 11. Summarized mechanism of Class I aldolases. Just as with L-proline, this mechanism proceeds through formation and collapse of an enamine intermediate.

The specific catalytic system to be studied is the asymmetric direct aldol condensation as mediated by L-prolinamide. Aldol condensations, specifically enantioselective condensations, have long

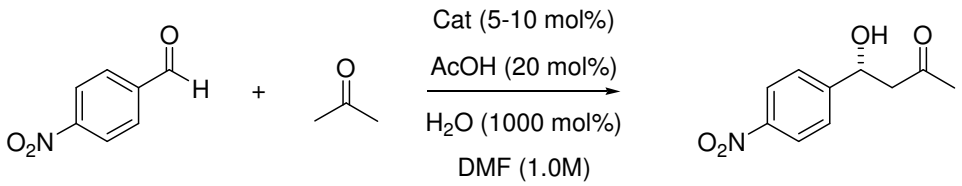
been of interest to the chemical community, in that they are of great synthetic, biochemical, and pharmaceutical use. Asymmetric Aldol condensations allow the skilled chemist to construct a vast array of stereochemically complex natural and nonnatural products, many of which have interesting and useful biochemical and pharmaceutical applications. L-prolinamide, like L-proline, is biomimetic. It is believed that L-prolinamide, like L-proline and type I aldolases, catalyzes aldol condensations via an enamine intermediate. (Figures 10,11). The enamine mechanism through which L-proline catalyzes these reactions is enantioselective, and tends to preferentially catalyze the reaction for the R enantiomer, making such a catalyst a useful tool for the synthetic chemist.[20]

This enantioselectivity also allows us to measure the efficiency of our catalyst, by detecting the enantiomeric excess, diastereomeric excess and regioselectivity (in some cases) of the preferred species, thus giving us an idea about the quality of the proline dendron system as a catalyst. Current L-prolinamide catalyzed systems exhibit 50-75% ee.[21] However, by coupling the catalytic properties of L-proline with a 2, 4-dicarboxamide based dendritic system, we hope to further enhance the enantioselectivity of this reaction.

Preliminary Results and Discussion

C2 Symmetric (bis-prolinamide) Dendrons

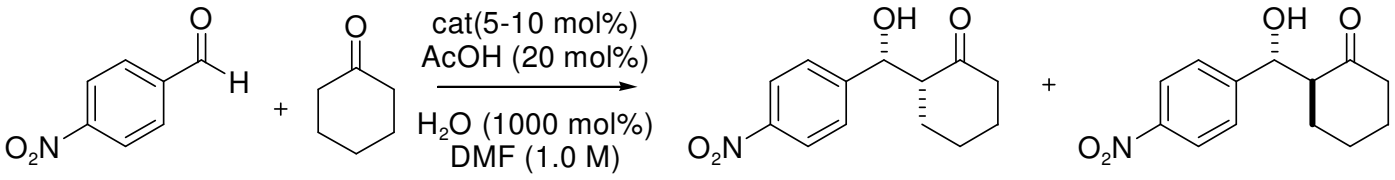
Direct aldol condensation of acetone and *p*-nitrobenzaldehyde.



Catalyst	mol %	Yield	Ee
G1	10	42%	65%
G2 Type I	5	24%	61%
G2 Type II	5	10%	51%

Table 1. Condensation of p-nitrobenzaldehyde and acetone as mediated by dendrimeric catalysts.

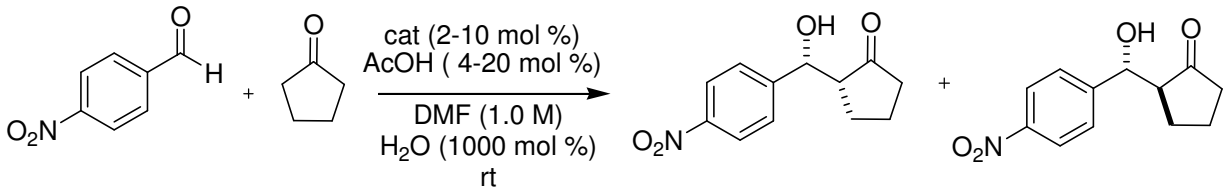
Direct aldol condensation of cyclohexanone and *p*-nitrobenzaldehyde



Cat.	Mol%	Yield	d.r.(syn:anti)	e.e. (syn)	e.e. (anti)
G1	10	90%	1:4.4	48%	59%
G2-I	5	73%	**1:15**	26%	**96%**
G2-II	5	69%	**1:6.5**	3%	**84%**

Table 2. Condensation of p-nitrobenzaldehyde and cyclohexanone as mediated by dendrimeric catalysts.

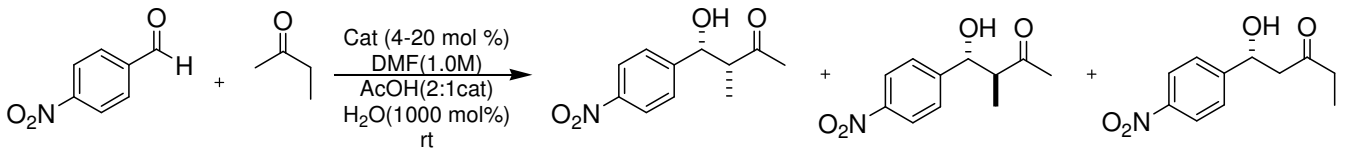
Direct aldol condensation of cyclopentanone and *p*-nitrobenzaldehyde



Cat	Mol%	Yield	d.r.(syn:anti)	ee (syn)	ee (anti)
G1	10	99%	2.6 : 1	20 %	64%
G1	4	87%	2.9 : 1	14 %	62%
G1	2	64%	2.7 : 1	16 %	60%
G2 Type I	2	87%	1 : 1.7	72%	92%
G2 Type II	2	87%	1 : 1.5	84%	92%

Table 3. Condensation of p-nitrobenzaldehyde and cyclopentanone as mediated by dendrimeric catalysts.

Direct aldol condensation of 2-butanone and *p*-nitrobenzaldehyde



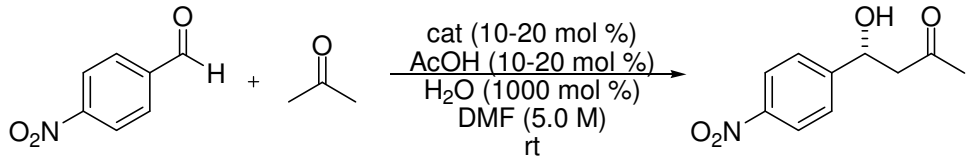
Catalyst	mol %	Combined yield	d.r. (*syn : anti*)	ee (*syn*)	ee (*anti*)	ee (methyl addition)	Regioselectivity (Me : Et addition)
G1	20	59%	1 : 4.0	68	68	50	1 : 3.0
G1	10	51%	1 : 4.0	68	58	56	1 : 4.6
G1	4	17%	1 : 4.5	74	66	51	1 : 1.0
G2 Type I	10	48%	**1 : 5.7**	**25**	**90**	66	**1 : 1.5**
G2 Type II	10	38%	**1 : 7.6**	**48**	**92**	42	**1 : 3.0**

Table 4. Condensation of p-nitrobenzaldehyde and 2-butanone as mediated by dendrimeric catalysts.

Desymmetrized (mono-prolinamide) Dendrons

Kazuhiko Mitsui

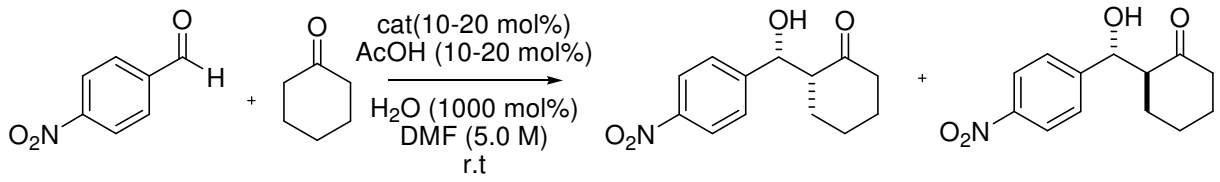
Direct aldol condensation of acetone and *p*-nitrobenzaldehyde.



Catalyst	mol %	Yield	Ee
G1	20	59%	36%
G2 Type I	10	50%	59%
G2 Type II	10	55%	45%

Table 5. Condensation of p-nitrobenzaldehyde and acetone as mediated by dendrimeric catalysts.

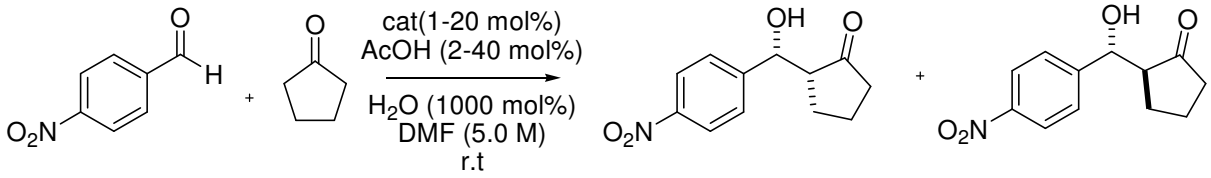
Direct aldol condensation of cyclohexanone and *p*-nitrobenzaldehyde



Cat.	Mol%	Yield	d.r.(syn:anti)	e.e. (syn)	e.e. (anti)
G1	20	92%	1:4.6	79%	78%
G2-I	10	87%	**1:24.5**	44%	**93%**
G2-II	10	87%	**1:14**	29%	**93%**

Table 6. Condensation of p-nitrobenzaldehyde and cyclohexanone as mediated by dendrimeric catalysts.

Direct aldol condensation of cyclopentanone and *p*-nitrobenzaldehyde



Cat	Mol%	Yield	d.r.(syn:anti)	ee (syn)	ee (anti)
G1	20	94%	2.5 : 1	4 %	26%
G1	10	98%	3.5 : 1	8%	44%
G1	4	67%	3.0 : 1	22 %	38%
G1	1	24%	3.4 : 1	8 %	38%
G2 Type I	2	95%	1 : 2.5	48%	90%
G2 Type II	2	81%	1 : 2.5	32%	88%

Table 7. Condensation of p-nitrobenzaldehyde and cyclopentanone as mediated by dendrimeric catalysts.

Preliminary findings show an increase in enantioselectivity and diastereoselectivity with larger dendron generations (Tables 2-4) along with a few other interesting trends. Furthermore, similar trends are seen with desymmetrized (mono-prolinamide) dendrons (tables 5-7). In the condensation with acetone (tables 1, 5), no substantial increase is observed in enantioselectivities, perhaps because of the

lack of steric bulk of acetone, which might help induce a facial preference in the transition state, and result in increased enantioselectivity. In the condensation with cyclohexanone (tables 2, 6), as the enantioselectivities for the preferred (*anti*) pair of enantiomers increases, there is a corresponding decrease in the enantioselectivities for the disfavored (*syn*) pair. In the condensation of *p*-nitrobenzaldehyde with cyclopentanone (tables 3, 7), in switching from first to second generation dendrons, there is an observed flip in the diastereoselectivity from *syn* selective (G1) to *anti* selective (G2). In the condensation with 2-butanone as the ketone (table 4), an increase in enantioselectivities for the *anti* pair of enantiomers is seen upon switching from first to second generation dendrons, and a decrease is seen in the enantioselectivities for the *syn* pair of enantiomers with an increase in dendron generation. However, no change in enantioselectivity is observed for the disfavored regioisomer (methyl addition). It is hypothesized that this augmentation in stereochemical selectivity is due to the increased cooperativity within the dendrimers. Further reactions will be examined to investigate the stereoselective scope of this reaction and the influence of the correlated motions within the synthesized dendrimers. Larger generations of dendrimers will be synthesized to confirm the correlation between dendrimer generation and coordinated cooperativity.

Conclusions

In summary, first and second generation dendrons were synthesized and used as catalysts in a series of asymmetric direct aldol condensations. Incorporation of a pyridine-2,6-dicarboxamide unit into these dendrons resulted in a coordinated cooperativity within the secondary structure, which was responsible for the stereoselective enhancements seen in asymmetric catalysis. Increasing dendrimer generation, and therefore increasing the amount of synchronized motions present, resulted in an enhancement of enantioselectivity and diastereoselectivity. These results indicate that such synchronized motions do contribute to the stereoselectivity of a catalytic reaction.

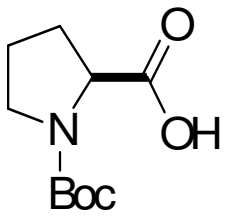
Furthermore, L-proline, in combination with this specific dendritic structure, provides a much better mimic of biological systems than previous work in the field. Because similar trends are seen with both mono- and bis-prolinamide systems, it can be deduced that the cooperativity is an effect of the secondary

structure of the dendron rather than an interaction between adjacent catalytic sites. Also, since the mole percent of proline was kept constant in increasing from first to second generation dendrons, these results cannot be attributed to a "concentration" effect either, whereby the selectivities increase due to an increase in the number of catalytic sites present at higher generations. It is reasonable to conclude that the increases observed in stereoselectivites can be attributed to the coordinated cooperativity inherent in the secondary structure of these dendrons. The structure and conformational cooperativity of the dendrimer makes it very similar to biological molecules such as enzymes, and the catalytic properties of proline are utilized in many natural enzymatic systems.[10,22] These types of biological mimics are still a relatively new development, and show great potential.

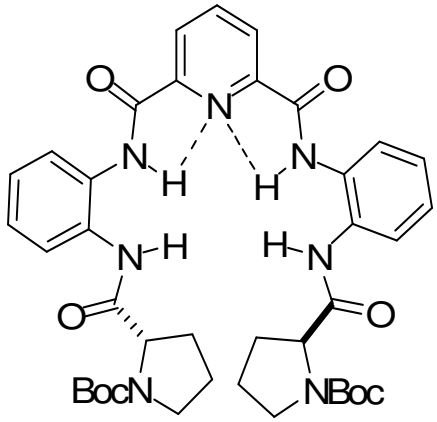
Experimental Section

General Notes

All NMR were run on a Bruker DPX 400 MHz NMR unless otherwise noted. All reactions run at ambient temperature and pressure unless otherwise noted. Dimethylformamide (DMF) was dried by distillation over sodium hydroxide, dichloromethane (CH_2Cl_2) was distilled from calcium hydride, Pyridine was distilled from calcium hydride. Thin Layer Chromatography was performed on glass backed plates with 60Å silica gel and a fluorescent indicator. Chromatographic separations were performed on silica gel 60 (230-400 mesh, 60 Å) using the solvents indicated.



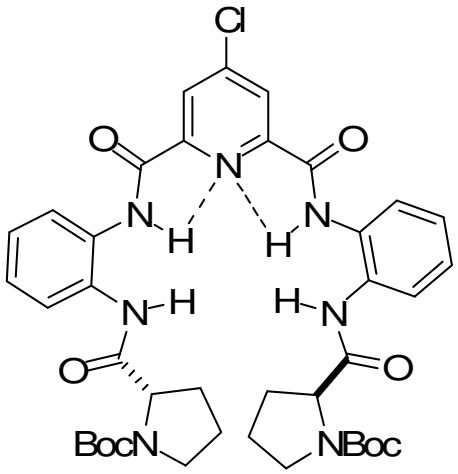
Boc-protected L-proline (*J. Org. Chem.* **2002**, *67*, 7162) . L-proline (11.10 mmol) was dissolved in H_2O (3 M) and tetrahydrofuran (1.5 M). Aqueous sodium hydroxide (10%, 2 M in L-proline) was added. Boc anhydride (16.65 mmol) was added portionwise, and the reaction mixture was allowed to stir for 12 h. THF was removed *in vacuo*. Remaining residue was washed with ethyl acetate, acidified to pH 2 and extracted with ethyl acetate. Organic extracts were combined, washed with water and brine, dried (Na_2SO_4) and concentrated *in vacuo* to give a white solid. (10.3 mmol, 93%). ^{1}H NMR ($CDCl_3$) δ 1.39-1.45 (m, 9H), 1.87-1.96 (m, 2H), 1.99-2.10 (m, 1H), 2.21-2.23 (m, 1H), 3.32-3.51 (m, 2H), 4.27 (m, 1H), 11.34 (broad singlet, 1H) ^{13}C NMR ($CDCl_3$) δ 24.30, 28.38, 30.82, 46.93, 59.06, 81.21, 156.15, 178.92.



1a

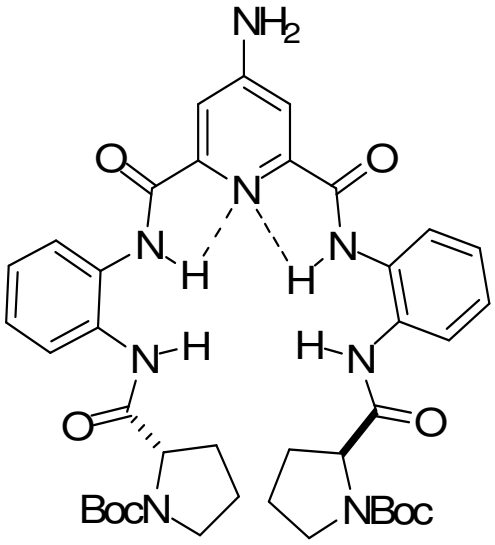
Boc-protected G1 dendron (1a). Under an atmosphere of nitrogen, boc-protected L-proline (10.33 mmol) was dissolved in tetrahydrofuran (0.2 M), and system was cooled to 0 ^{o}C with an ice bath. Triethylamine was added (15.50 mmol). Ethyl chloroformate was added dropwise and solution turned cloudy. The reaction mixture was allowed to stir for 1.5 h. Phenylene diamine (9.30 mmol) was dissolved in tetrahydrofuran (1.0 M) and added quickly. The reaction mixture was allowed to stir for 6 h. Pyridine-2,6-carboxylic acid chloride (5.17 mmol) was dissolved in dichloromethane (1.0 M) and added dropwise. The reaction mixture was warmed to room temperature and allowed to stir for 12 h overnight. Reaction showed completion by TLC. Solvents were removed *in vacuo*, residue was dissolved in dichloromethane, washed with 1 M hydrochloric acid, saturated soduium bicarbonate, brine, dried (Na_2SO_4) and concentrated in vacuo. Purified by column chromatography (1-5% methanol/chloroform on silica gel). (4.80 mmol, 96%) ^{1}H NMR (DMSO, 80 ^{o}C) δ 1.20 (s, 18H), 1.60-1.64 (m, 4H), 1.82-1.88 (m, 2H), 1.95-2.02 (m, 2H), 3.07-3.20 (m, 4H), 4.17 (dd, J_1= 8.4 Hz, J_2= 4.4 Hz), 7.27-7.32 (m, 4H), 7.62 (d, *J*=3.2 Hz, 2H), 7.80 (t, *J*=4.8 Hz, 2H), 8.34 (dd, J_1= 8.8 Hz, J_2= 6.8 Hz, 1H), 8.42 (d, *J*=7.2 Hz, 2H), 9.54 (s, 1H (NH)), 10.87 (s, 1H (NH)). ^{13}C NMR (DMSO, 80 ^{o}C) δ 23.83, 28 35, 46.94, 61.12, 79.23, 125.18, 125.56, 125.73, 125.82, 126.23, 130.58, 131.49, 140.58, 149.04, 162.11, 172.46.

Synthesis of G2 type I dendron.



2a

Boc-protected G-1(Cl) dendron (2a). Under an atmosphere of nitrogen, boc-protected L-proline (10.33 mmol) was dissolved in tetrahydrofuran (0.2 M), and system was cooled to 0 ^{o}C with an ice bath. Triethylamine was added (15.50 mmol). Ethyl chloroformate was added dropwise and solution turned cloudy. The reaction mixture was allowed to stir for 1.5 h. Phenylene diamine (9.30 mmol) was dissolved in tetrahydrofuran (1.0 M) and added quickly. The reaction mixture was allowed to stir for 6 h. 4-Chloropyridine-2,6-carboxylic acid chloride (5.17 mmol) was dissolved in dichloromethane (1.0 M) and added dropwise. The reaction mixture was warmed to room temperature and allowed to stir for 12 h overnight. Reaction showed completion by TLC. Solvents were removed *in vacuo*, residue was dissolved in dichloromethane, washed with 1 M hydrochloric acid, saturated sodium bicarbonate, brine, dried (Na_2SO_4) and concentrated *in vacuo*. Purified by column chromatography (1-5% methanol/chloroform on silica gel). (2.63 mmol, 26%). ^{1}H NMR (DMSO, 80 ^{o}C, 500 MHz) δ 1.22 (s, 18 H), 1.60-1.64 (m, 4H), 1.85-1.87 (m, 2H), 1.97-2.00 (m, 2H), 3.09-3.13(m, 2H), 3.16-3.19 (m, 2H), 4.16 (dd, J_1= 8.5 Hz, J_2=4.0 Hz, 2H), 7.28-7.30 (m, 4H), 7.62 (q, J_1=5.8 Hz, J_2=2.5 Hz, 2H), 7.74 (q, J_1=6 Hz, J_2= 2.5 Hz, 2H), 8.37 (s, 2H), 9.42 (s, 1H (NH)), 10.80 (s, 1H (NH)) ^{13}C NMR (DMSO, 80 ^{o}C, 500 MHz) δ 23.87, 28.39, 46.99, 55.11, 61.15, 79.33, 125.32, 125.81, 126.53, 130.25, 131.74, 147.47, 150.88, 161.05, 172.41.

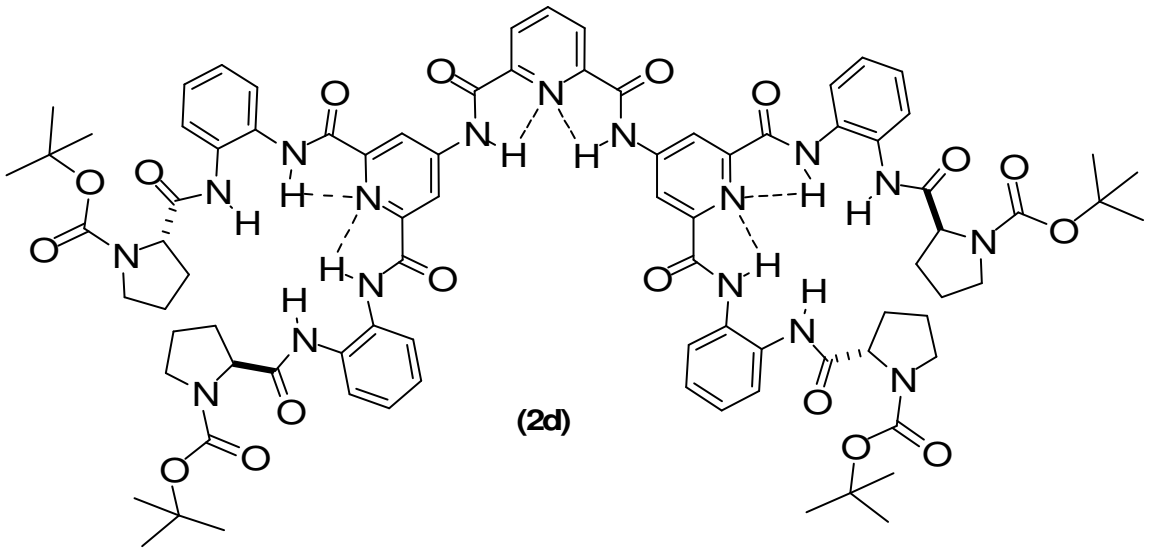


2c

Boc-protected G-1(NH_2) dendron (2c).

(2b). **2a** (2.60 mmol) was dissolved in dimethylformamide (0.2M) under an atmosphere of nitrogen. Sodium azide was added (25.6 mmol) and a reflux condenser attached. The system was heated to 60 ^{o}C and monitored by TLC. Reaction showed completion after 44 h. A small amount of water and brine was added. Organic layer was extracted, washed with brine, dried (Na_2SO_4) and concentrated in vacuo. Crude solid used directly in 1c. (2.57 mmol, 99%)

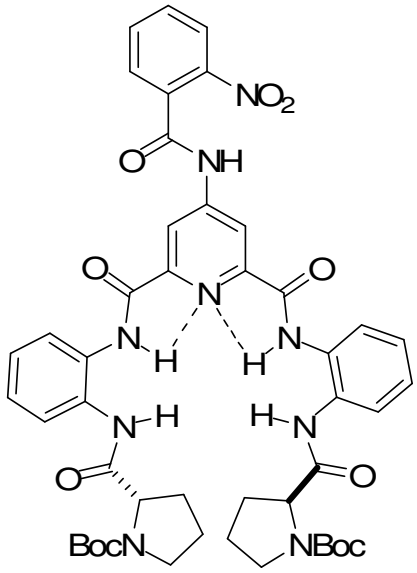
(2c). 2b (2.57 mmol) was dissolved in ethy acetate (0.1M) and palladium on carbon (10 % cat) was added. Reaction was put under hydrogen (1 atm) and allowed to stir for 12 h overnight. Reaction was filtered through celite and concentrated *in vacuo*. Purified by column chromatography (2-5% methanol/chloroform) (2.57 mmol, quant.) ^{1}H NMR (DMSO, 80 ^{o}C, 500 MHz) δ 1.24 (s, 18H), 1.54-1.57 (m, 2H), 1.62-1.64 (m, 2H), 1.80-1.82 (m, 2H), 1.96-2.00 (m, 2H), 3.12-3.17 (m, 4H), 4.13 (q, *J*= 4.0 Hz, 3H), 6.59 (s, 1H(NH)), 7.23-7.27 (m, 4H), 7.53 (s, 2H), 7.55 (d, *J*=6.5 Hz, 2H), 7.78 (d, *J*=7.0 Hz, 2H), 9.48 (s, 1H(NH)), 10.67 (s, 1H(NH)) ^{13}C NMR (DMSO, 80 ^{o}C, 500 MHz) δ 23.80, 28.41, 30.95, 46.94, 61.16, 79.25, 109.61, 125.35, 125.82, 131.09, 149.56, 153.97, 157.96, 162.99, 172.51 MS: 779 (M + Na).



(2d)

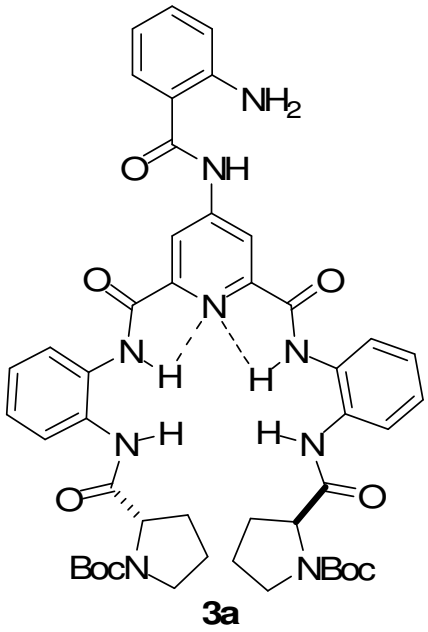
Boc-protected G-2 dendron (2d). DMAP (0.22 mmol) and 2c (1.12 mmol) were dissolved in dichloromethane (0.2M) under an atmosphere of nitrogen and cooled to 0 ^{o}C using an ice bath. Pyridine (0.2M) was added. Pyridine-2,6-dicarboxylic acid chloride was dissolved in dichloromethane (1.0 M) and added dropwise. Reaction mixture was allowed to stir 16 h (showed completion by TLC). Reaction mixture was washed with 1 M hydrochloric acid, saturated sodium bicarbonate, and brine. Organic layer was dried (Na_2SO_4) and concentrated. Residue purified by column chromatography (5-30% methanol/diethyl ether). (0.48 mmol, 85%) ^{1}H NMR (DMSO, 80 ^{o}C) δ 1.20 (s, 36H), 1.54-1.63 (m, 8H), 1.82-1.86 (m, 4H), 1.96-1.98 (m, 4H), 3.09-3.16 (m, 8H), 4.14-4.16 (m, 4H), 7.28-7.32 (m 8H), 7.59 (d, *J*=7.2 Hz, 4H), 7.83 (d, *J*=7.2 Hz, 4H), 8.55 (t, *J*=8.0 Hz, 1H), 8.42 (d, *J*=8.0 Hz, 2H), 9.06 (s, 4H), 9.58 (s, 1H (*NH*)), 10.89 (s, 1H(*NH*)), 11.64 (s, 1H(*NH*)) 13C NMR (DMSO, 80 oC, 500 MHz) δ 23.87, 28.41, 31.01, 46.99, 61.12, 79.23, 115.86, 125.30, 125.75, 125.84, 126.14, 127.01, 130.79, 131.45, 140.71, 148.83, 149.23, 150.49, 154.00, 162.22, 163.65, 172.52 MS: 1668 (M + Na).

Synthesis of G2 type II dendron (3)



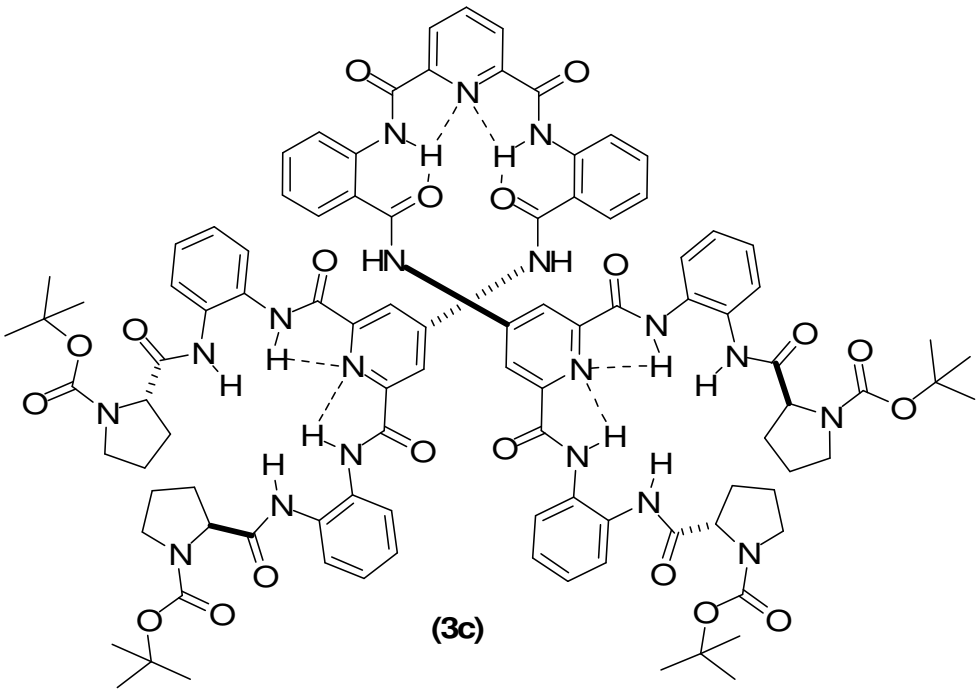
3a

Boc-protected G-I type II (NO_2) dendron (3a). 2c (0.84 mmol) and dimethylaminopyridine (0.17 mmol) were dissolved in dichloromethane (0.2 M) under an atmosphere of nitrogen. System was cooled to 0 ^{o}C in an ice bath and pyridine (0.2 M) was added. 2-nitrobenzoic acid chloride was dissolved in dichloromethane (1 M) and added dropwise. The reaction mixture was allowed to warm to room temperature. (Incomplete by TLC after 2 h). Reaction mixture was cooled to 0 ^{o}C with an ice bath and additional 0.42 mmol of *ortho*-nitrobenzoic acid chloride was added. The reaction was allowed to warm to room temperature and stir for 8 h (complete by TLC). Reaction was quenched with water, washed with 1 M hydrochloric acid, saturated sodium bicarbonate, and brine. Organic layers were dried (Na_2SO_4) and concentrated *in vacuo*. Used as a crude solid (0.70 mmol, 84%) ^{1}H NMR (DMSO, 80 ^{o}C) d 1.27 (s, 18 H), 1.55-1.63 (m, 4H), 1.80-1.85 (m, 2H), 1.96-1.99 (m, 2H), 3.08-3.16 (m, 4H), 4.13-4.15 (t, J=4.0 Hz, 2H), 7.27 (m, 4H), 7.56-7.58 (m, 2H), 7.75-7.77 (m, 2H), 7.79-7.85 (m, 2H), 7.90-7.92 (m, 1H), 8.17-8.22 (m, 1H), 8.66 (s, 2H), 9.52 (s, 1H (NH)), 10.82 (s, 1H(NH)), 11.32 (s, 1H (NH)) 13C NMR (DMSO, 80 oC), δ 28.27, 60.85, 68.61, 71.15, 79.27, 114. 84, 115.85, 146.68, 156. 39 MS: 928 (M + Na)



3a

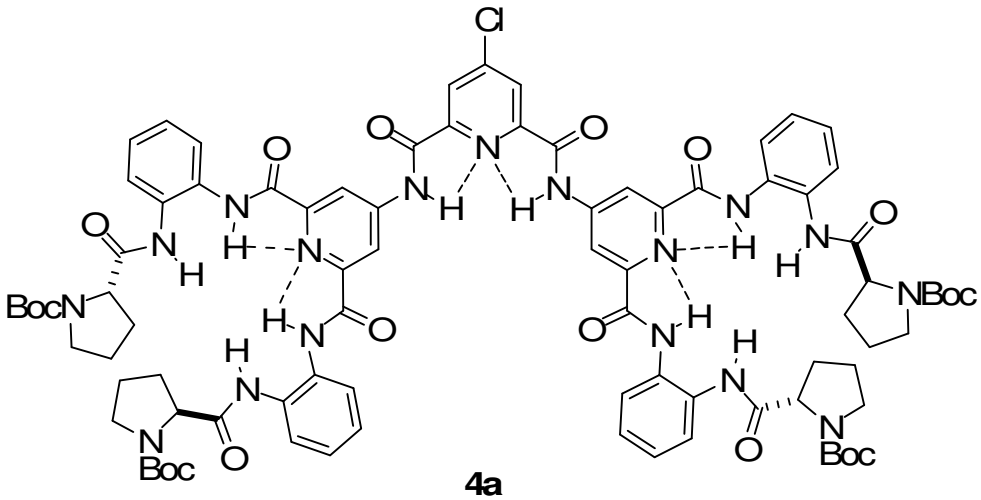
Boc-protected G-I type II (NH_2) dendron (3b). Crude solid **(3a)** was dissolved in methanol (0.1 M) and palladium on carbon was added (10 % cat). System was put under hydrogen (1 atm) and allowed to stir for 20 h. Reaction was filtered through celite and purified by column chromatography (1-3% methanol/chloroform) to give a yellow solid. (0.34 mmol, 48 %) ^{1}H NMR (DMSO, 80 ^{o}C, 500 MHz) δ 1.20 (s, 18H), 1.55-1.65 (m, 4H), 1.81-1.84 (m, 4H), 1.97-2.01 (m, 2H), 3.11-3.17 (m, 4H), 4.14 (dd, J_1=8.5 Hz, J_2=4.5 Hz, 2H), 6.63 (t, J=7.5 Hz, 1H), 6.82 (d, J=8.5 Hz, 1H), 7.24-7.30 (m, 5H), 7.59 (d, J=6.5 Hz, 2H), 7.77-7.80 (m 3H), 8.20 (m, 2H), 9.49 (s, 1H (NH)), 10.79 (s, 1H (NH)) ^{13}C NMR (DMSO, 80 ^{o}C, 500 MHz) δ 28.40, 46.97, 61.15, 79.27, 115.33, 125.89, 125.97, 126. 01, 126.12, 150.03, 150.33, 162.31.



(3c)

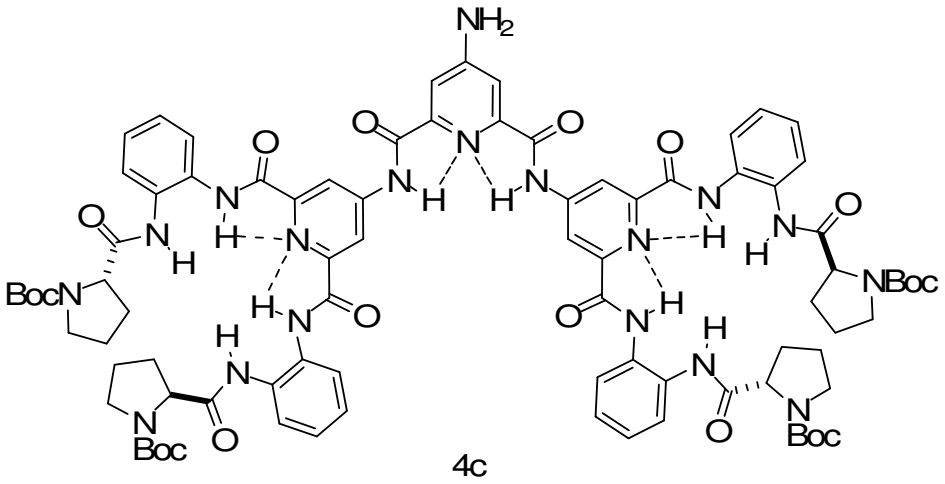
Boc-protected G-2 type II dendron (3c). 3b (0.68 mmol) and dimethylaminopyridine (0.14 mmol) were dissolved in dichloromethane (0.2 M) and pyridine (0.2M) under an atmosphere of nitrogen. Reaction mixture was cooled to 0 ^{o}C in an ice bath. Pyridine-2,6-dicarboxylic acid chloride (0.34 mmol) was dissolved in dichloromethane (1M) and added dropwise. The reaction mixture was warmed to room temperature and allowed to stir 18 h. Reaction mixture was washed with 1 M hydrochloric acid, saturated sodium bicarbonate, and brine. Organic layer was dried (Na_2SO_4) and concentrated *in vacuo*. Residue was purified by column chromatography (5-20 % methanol/diethyl ether) (0.190 mmol, 56%) ^{1}H NMR (DMSO, 80 ^{o}C, 500 MHz) δ 1.20 (s, 36H), 1.57-1.66 (m, 8H), 1.82-1.85 (m, 4H), 1.97-2.01 (m, 4H), 3.09-3.16 (m, 8H), 4.14-4.16 (q, *J*=4.0 Hz, 4H), 7.21 (t, *J*=7.5 Hz, 2H), 7.29-7.36 (m, 8H), 7.48 (t, *J*= 8.0 Hz, 2H), 7.59 (d, *J*=7.5 Hz, 4H), 7.79 (d, *J*=8.0 Hz, 2H), 7.86 (d, *J*=7.5 Hz, 4H), 8.30-8.34 (m, 3H), 8.39 (d, *J*=7.0 Hz, 2H), 8.60 (s, 4H), 9.57 (s, 1H (*NH*)), 10.72 (s, 1H (*NH*)), 10.89 (s, 1H (*NH*)), 11.95 (s, 1H, (*NH*)). ^{13}C NMR (DMSO, 80 ^{o}C, 500 MHz) δ 23.86, 28.39, 31.01, 46.93, 61.10, 79.23, 115.52, 123.14, 124.37, 124.84, 125.30, 125.48, 125.95, 129.42, 130.97, 132.62, 137.61, 149.31, 149.71, 149.86, 153.96, 161.85, 161.92, 167.82, 172.65.

Synthesis of G-3 type I dendron.



4a

Boc protected G-2 type I (Cl) dendron (4a). 2c (1.32 mmol) and DMAP (0.2 eq) were dissolved in dichloromethane (0.1M) under an atmosphere of nitrogen. System was cooled to 0 ^{o}C with an ice bath and pyridine (0.1M) was added. 4-chloro pyridine-2,6-dicarboxylic acid chloride (0.662 mmol, 0.5 eq) was added dropwise, and reaction was allowed to warm to room temperature and stirred overnight (19.5 h). Reaction mixture was washed with 1M HCl, sat. $NaHCO_3$, brine, and dried (Na_2SO_4). Purified by column chromatography (5-15% methanol/diethyl ether) to give 0.691 g (62%) yield of yellow solid. ^{1}H NMR (DMSO, 80 ^{o}C) δ 1.18 (s, 36 H), 1.53-1.63 (m, 8H), 1.81-1.86 (m, 4H), 1.93-2.00 (m, 4H), 3.06-3.17 (m, 8H), 4.15 (dd, J_1 = 8.0 Hz, J_2 = 4.4 Hz, 4H), 7.26-7.32 (m, 8H), 7.59 (d, J=4.8 Hz, 4H), 7.82 (d, J=6.8 Hz, 4H), 8.52 (s, 2H), 9.03 (s, 4H), 9.59 (s, 1H (NH)), 10.88 (s, 1H (NH)), 11. 61 (s, 1H (NH)) ^{13}C NMR (DMSO, 80 ^{o}C) δ 28.37, 79.20, 115.72, 125.91, 150.47, 162.04, 162.52.



4c

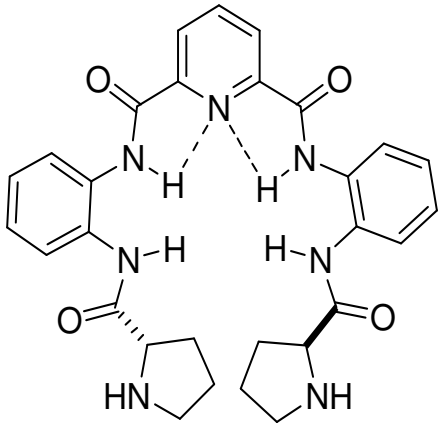
Boc protected G-2 type I (NH_2) dendron 4c.

(4b). 4a (.4118 mmol) was dissolved in DMF. Sodium azide (4.118 mmol, 10 eq) was added, system was put under nitrogen and allowed to stir 39 h. Reaction mixture was washed with water, brine, and dried (Na_2SO_4). Crude solid used in synthesis of **4c**.

4c. Crude solid from **4b** was dissolved in Ethyl Acetate (0.1M). Palladium on carbon (10 % cat.) was added. System flushed with hydrogen gas, and a balloon was attached. Allowed to stir overnight (20h). Reaction was filtered through celite and concentrated *in vacuo*. Purified by column chromatography (3-5% methanol/chloroform) to give a yellow solid (0.240 g, 30% over 2 steps) ^{1}H NMR (DMSO, 80 ^{o}C) δ 1.20 (s, 36 H), 1.57-1.65 (m, 8H), 1.79-1.87 (m, 4H), 1.93-2.00 (m, 4H), 3.05-3.17 (m, 8H), 4.15 (dd, J_1= 8 Hz, $_{J2}$= 4 Hz, 4H), 6.82 (s, 2H), 7.26-7.32 (m, 8H), 7.57-7.59 (m, 4H), 7.65 (s, 2H), 7.82 (d, J = 6 Hz, 4H), 9.03 (s, 4H), 9.59 (s, 1H (NH)), 10.87 (s, 1H (NH)), 11.46 (s, 1H, (NH)) ^{13}C NMR (DMSO, 80 ^{o}C) δ 28.36, 46.95, 61.07, 79.21, 115.63, 125.70, 125.91, 126.19, 149.20, 149.33, 150.32, 162.16, 164.36.

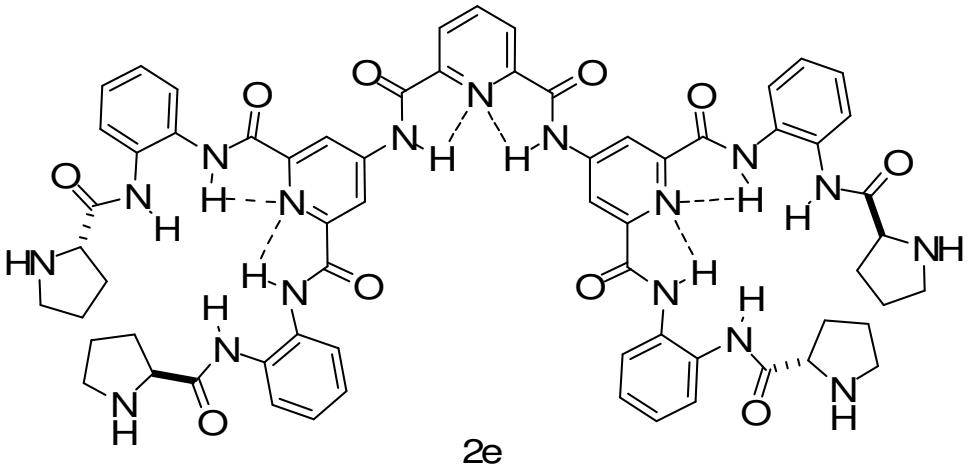
Dendrimer Deprotection

Generalized deprotection procedure. Dendrons were dissolved in dichloromethane (0.1M) under an atmosphere of nitrogen. Anisole was added (1M) and system was cooled to 0 ^{o}C with an ice bath. Trifluoroacetic acid (0.1M) was distilled and added dropwise. Reaction mixture was allowed to warm to room temp and stirred for 4-6h, (complete by TLC). Solvents were evaporated, and residue was triturated with chloroform, and allowed to stir overnight (8-16 h) or until color disappeared. (95-99%)



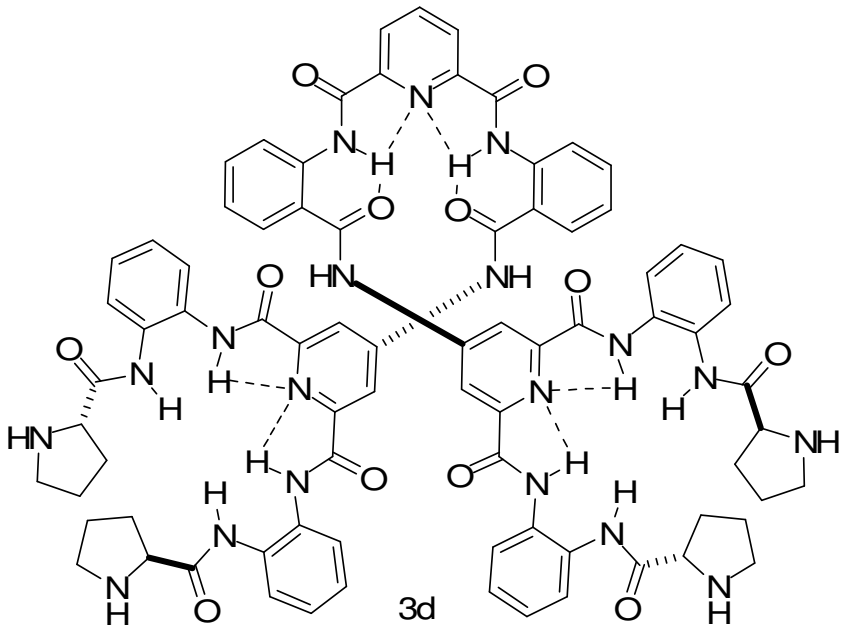
1b

G1 dendron (1b). ^{1}H NMR (DMSO, 80 ^{o}C, 500 MHz) δ 1.43-1.53 (m, 4H), 1.70-1.74 (m, 2H), 1.85-1.92 (m, 2H), 2.62-2.67 (m, 2H), 2.73-2.77 (m, 2H), 3.70 (dd, J_1= 9.0 Hz, J_2= 5.5 Hz, 2H), 7.21-7.25 (m, 2H), 7.27-7.31 (m, 2H), 7.60 (dd, J_1= 8.0 Hz, J_2= 1.5 Hz, 2H), 7.85 (dd, J_1=8.0 Hz, J_2= 1.5 Hz, 2H), 8.31 (m, 1H), 8.40 (d, J= 4.5 Hz), 10.92 (s, 1H (NH)) ^{13}C NMR (DMSO, 80 ^{o}C, 500 MHz) δ 25.84, 30.65, 46.85, 61.27, 70.43, 123.48, 124.99, 125.45, 126.92, 126.97, 129.31, 133.18, 140.43, 149.10, 162.47, 173.80.



2e

G2 type I dendron (2e). (0.059 mmol, 96 %) ^{1}H NMR (DMSO, 80 ^{o}C) d 1.72-1.81 (m), 1.98-2.07 (m), 2.20-2.29 (m), 3.12 (t, *J*=3.2 Hz), 3.72 (broad singlet), 4.38 (t, *J*=7.6 Hz), 7.32-7.39 (m), 7.62-6.65(m), 7.69-7.73(m), 8.42 (dd, J_1= 8.4, J_2=7.2 Hz), 8.54 (d, *J*=7.6 Hz), 9.03 (broad singlet), 10.66 (s),11.63 (s) ^{13}C NMR (DMSO, 80 ^{o}C, 500 MHz) δ 23.82, 29.91, 46.23, 60.28, 115.85, 125.74, 126.47, 126.74, 126.87, 130.95, 131.84, 148.82, 148.97, 150.71, 162.58, 163.66, 168.02 MS: 1266 $(M + Na)^{+}$.

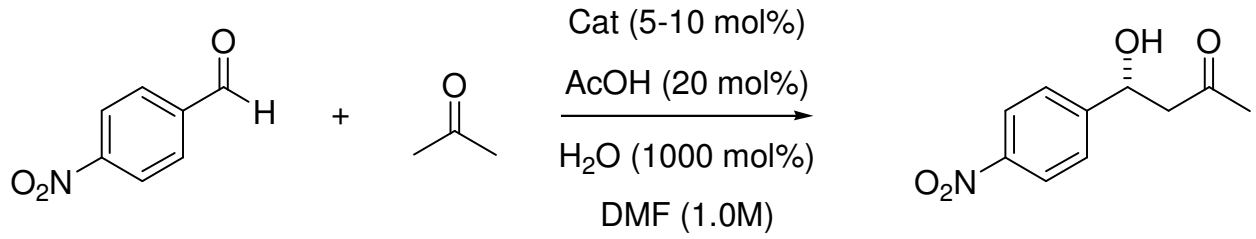


3d

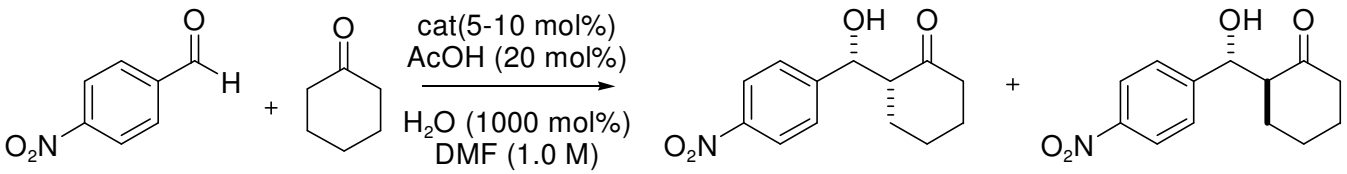
G2 type II dendron (3d). (.102 mmol, 95%) ^{1}H NMR (DMSO, 80 ^{o}C) d 1.61-1.79 (m), 1.93-2.04 (m), 2.13-2.24 (m), 3.02-3.14 (m), 3.91 (broad singlet), 4.37 (t, *J*=7.6 Hz), 7.24 (t, *J*=7.6 Hz), 7.32-7.39 (m), 7.47-7.51 (m), 7.65-7.68 (m), 7.79 (dd, J_1=7.6, J_2=1.2 Hz), 8.14 (d, *J*=8 Hz), 8.27-8.35 (m), 8.58 (s), 9.93 (broad singlet), 10.45 (s), 10.95 (s), 11.79 (s) ^{13}C NMR (DMSO, 80 ^{o}C, 500 MHz) δ 23.86, 29.76, 46.17, 60.31, 115.65, 123.39, 124.53, 125.37, 125.57, 125.97, 126.43, 126.53, 126.61, 129.51, 131.17, 131.21, 132.62, 137.42, 149.29, 149.53, 150.13, 158.86, 159.13, 161.99, 162.28, 167.87, 168.12 MS: 1505 $(M + Na)^{+}$.

Catalysis: Asymmetric Direct Aldol Condensations

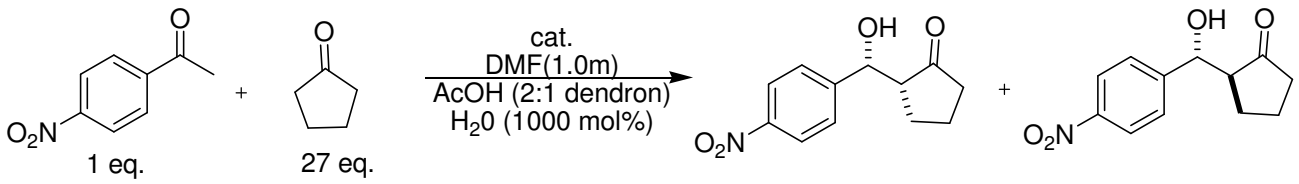
Generalized procedure for aldol condensations. Dendrons (2-20 mol%), were stirred in dimethylforamide for 10 min. Acetic acid (4-40 mol%) was added, and the mixture was allowed to stir for 10 min. Distilled ketone (27.0 eq) was added, and the mixture was allowed to stir for 15 min. Water (10.0 eq) and aldehyde (1 eq) were added. The reaction was allowed to stir for 24 h. The reaction mixture was quenched with saturated ammonium chloride, and stirred for 30 min. The remaining residue was dissolved in water, and washed with diethyl ether (4 x 20 mL). Organic layers were combined and washed with water and brine. Organic layers were dried (Na_2SO_4) and concentrated *in vacuo*. Purified by column chromatography (ethyl acetate/petroleum ether or ethyl acetate/hexanes)



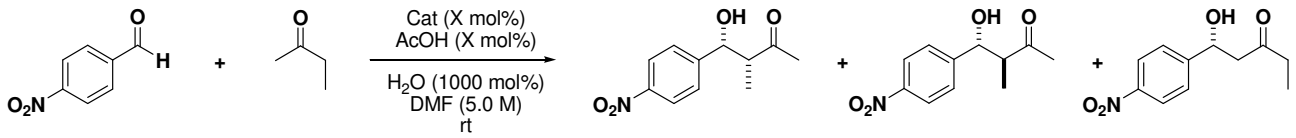
Condensation of p-nitrobenzaldehyde with acetone. Dendrons (5 mol% in L-prolinamide), were stirred in dimethylformamide for 10 min. Acetic acid (0.1 mmol) was added, and the mixture was allowed to stir for 10 min. Distilled acetone (13.5 mmol) was added, and the mixture was allowed to stir for 15 min. Water (5.0 mmol) and p-nitrobenzaldehyde (0.5 mmol) were added. The reaction was allowed to stir for 24 h. The reaction mixture was quenched with saturated ammonium chloride, and stirred for 30 min. The remaining residue was dissolved in water, and washed with diethyl ether (4 x 20 mL). Organic layers were combined and washed with water and brine. Organic layers were dried (Na_2SO_4) and concentrated *in vacuo*. Purified by column chromatography (20-50% Ethyl acetate/hexanes). (10-42%). HPLC: Chiralpac OB, 1 mL/min, 10% isopropanol/hexanes 49-76 % e.e.



Condensation of p-nitrobenzaldehyde with cyclohexanone. Dendrons (5 mol% in L-prolinamide), were stirred in dimethylformamide for 10 min. Acetic acid (0.1 mmol) was added, and the mixture was allowed to stir for 10 min. Distilled cyclohexanone (13.5 mmol) was added, and the mixture was allowed to stir for 15 min. Water (5.0 mmol) and *p*-nitrobenzaldehyde (0.5 mmol) were added. The reaction was allowed to stir for 24 h. The reaction mixture was quenched with saturated ammonium chloride, and stirred for 30 min. The remaining residue was dissolved in water, and washed with diethyl ether (4 x 20 mL). Organic layers were combined and washed with water and brine. Organic layers were dried (Na_2SO_4) and concentrated *in vacuo*. Purified by column chromatography (10-40% ethyl acetate/petroleum ether). (69-94%). HPLC: anti: Chiralpac OD, 1 mL/min, 20% isopropanol/hexanes 55-96 % e.e. HPLC: syn: Chiralpac OJ, 1 mL/min, 20% isopropanol/hexanes 3-48 % e.e. ^{1}H NMR ($CDCl_3$) 1.82-1.87(m, 1H), 2.10-2.16 (m, 4H), 2.34-2.42 (m, 1H), 2.49-2.54 (m, 1H), 2.58-2.64 (m, 1H), 3.21 (s, 0.14H), 4.09 (s, 0.86H), 4.91 (dd, J_1=8.0, J_2= 3.2 Hz, 0.87H), 5.49 (s, 0.13H), 7.48 (d, J=8.4Hz, 2H), 8.21(dd, J_1=8.4, J_2=1.6 Hz, 2H)



Condensation of p-nitrobenzaldehyde with cyclopentanone. Dendrons (20-4 mol% in L-prolinamide), were stirred in dimethylformamide for 10 min. Acetic acid (0.20-0.04 mmol) was added, and the mixture was allowed to stir for 10 min. Distilled cyclohexanone (13.5 mmol) was added, and the mixture was allowed to stir for 15 min. Water (5.0 mmol) and p-nitrobenzaldehyde (0.5 mmol) were added. The reaction was allowed to stir for 4-24 h. The reaction mixture was quenched with saturated ammonium chloride, and stirred for 30 min. The remaining residue was dissolved in water, and washed with diethyl ether (4 x 20 mL). Organic layers were combined and washed with water and brine. Organic layers were dried (Na_2SO_4) and concentrated *in vacuo*. Purified by column chromatography (20-40% Ethyl acetate/petroleum ether). (64-99%). HPLC: syn+anti: Chiralpac IA, 1 mL/min, 5.0% isopropanol/hexanes 16-92 % e.e.



Condensation of p-nitrobenzaldehyde with 2-butanone. Dendrons (8-40 mol% in L-prolinamide), were stirred in dimethylforamide for 10 min. Acetic acid (0.08-0.4 mmol) was added, and the mixture was allowed to stir for 10 min. Distilled cyclohexanone (13.5 mmol) was added, and the mixture was allowed to stir for 15 min. Water (5.0 mmol) and p-nitrobenzaldehyde (0.5 mmol) were added. The reaction was allowed to stir for 24 h. The reaction mixture was quenched with saturated ammonium chloride, and stirred for 30 min. The remaining residue was dissolved in water, and washed with ethyl acetate (4 x 20 mL). Organic layers were combined and washed with water and brine. Organic layers were dried (Na_2SO_4) and concentrated *in vacuo*. Purified by column chromatography (40-100% Ethyl acetate/petroleum ether). (17-59%). HPLC: syn+anti: Chiralpac AS-H, 1 mL/min, 5.0% isopropanol/hexanes 32-92 % e.e. ^{1}H NMR ($CDCl_3$) δ 0.88 (d, *J*=7.6 Hz, 3H), 2.18 (s, 3H), 2.78-2.92 (m, 1H), 3.27 (s, 1H (OH)), 4.84 (d, *J*= 7.6 Hz, 0.85 H), 5.25 (d, *J*=2.4 Hz, 0.14 Hz), 7.49 (d, *J*=8.8 Hz, 2H), 8.18 (d, *J*= 8.4 Hz, 2H) HPLC: methyl addition: Chiralpac AS-H, 1 mL/min, 20% isopropanol/hexanes 42-66 % e.e. ^{1}H NMR ($CDCl_3$) δ 1.08 (t, *J*=9.0 Hz, 3H), 2.43-2.50 (m, 2H), 2.76-2.83 (m, 2H), 2.26 (q, J_1=10 Hz, J_2= 5Hz, 1H), 7.53 (d, *J*=11 Hz, 2H), 8.20 (d, *J*=11 Hz, 2H).

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References

1. Voet, D.; Voet, J. G. *Biochemistry 3rd ed*. John Wiley & Sons: Hoboken NJ, 2004.

2. Szwajkajzer, D.; Carey, J. *Biopolymers*, **1997**, *44*, 181.

3. Yon, J.M.; Perahia, D.; Ghelis, C. *Biochimie*. **1998**, *80*, 33.

4. a. Baldwin, J.; Chothia, C. *J. Mol. Biol*. **1979**, *129,* 175.

   b. Kneipp, et. al. *J. Mol. Biol*. **2006**, *356*, 335.

5. a. Green, M., et. al. *Angew. Chem. Int. Ed.* **1999***, 38*, 3138.

   b. Lockman, J.W.; Paul, N.M.; Parquette, J. *Prog. Polym. Sci*. **2005**, *30*, 423.

6. Wand, A.J., et. al. *Nat. Struct Biol*. **2001**, *8*, 926.

7. Guilbert, C.; Perahia, D.; Mouawad, L. *Comput. Phys. Commun*. **1995**, *91*, 263.

8. Green, M., et. al. *Angew. Chem. Int. Ed.* **1999***, 38*, 3138.

9. Newkone, G.R.; Moorefield, C.N.; Voglle, F. *Dendrons and Dendrimers*, Weley-VCH, Weinheim, Germany. 2001.

10. Huang, B; Prantil, M. A.; Gustafson, T. L.; Parquette, J. R. *J. Am. Chem. Soc.* **2003**, *125*, 14518-14530.

11. Astruc, D.; Chardac, F. *Chem. Rev.* **2001**, *101*, 2991-3023.

12. Parquette, J.R. *C.R. Chimie.* 6 (2003).

13. Liang, C.; Frechet, J. M. J. *Prog.Polym. Sci*. **2005**, *30*, 385.

14. Francavilla, C.; Drake, M. D.; Bright, F. V.; Detty, M. R. *J. Am. Chem. Soc*. **2001**, *123*, 57

15. Kofoed, J.; Reymond, J. L. *Current Opinion in Chemical Biology.***2005,** *9,* 656.

16. Hecht S; Frechet, J. *J. Am. Chem. Soc.* **2001**, *123*, 6959.

17. Liu, L; Breslow, R. *J. Am. Chem. Soc*. **2003**, *125*, 12110.

18. Hadad, C.; Parquette, J.R.; et. al. *Tetrahedron*, **2003**, *59*, 3917.

19. Hofacker, A. L.; Parquette, J. R. *Angew. Chem. Int. Ed*. **2005**, *44*, 1053

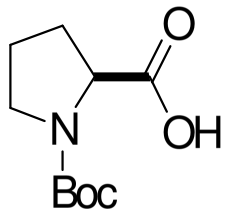
20. Palomo, C.; Oiarbide, M.; Garcia, J. M. *Chem. Eur. J.* **2002,** *8*, 37-44.

21. Chen, J. *Org. Lett.* **2005**, *7*, 4523.

22. List, B. *Tetrahedron.* **2002**, *58*, 5573-5590.

Appendix:

Select ^{1}H and ^{13}C NMR spectra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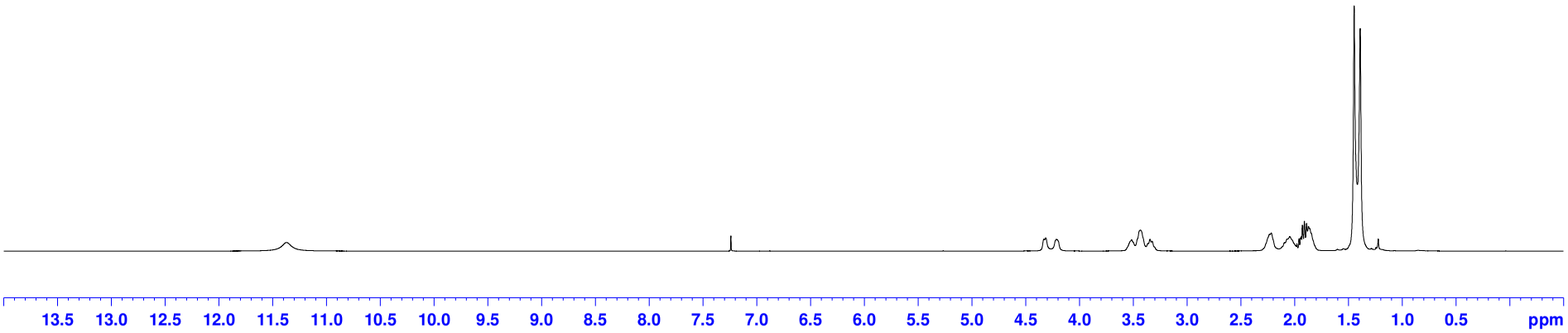
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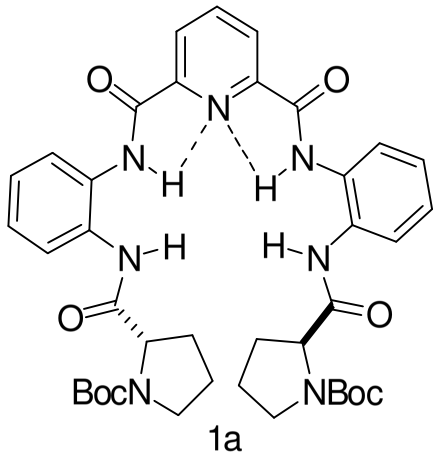
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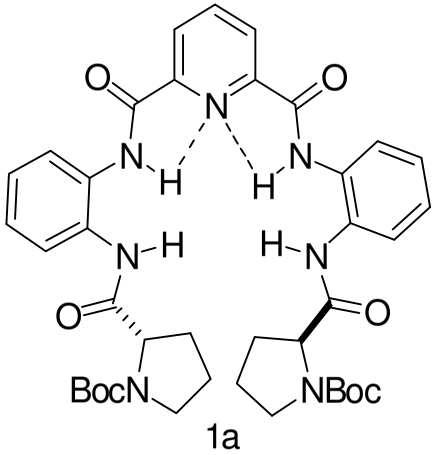
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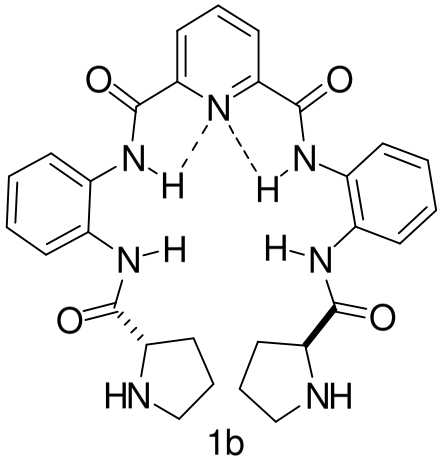
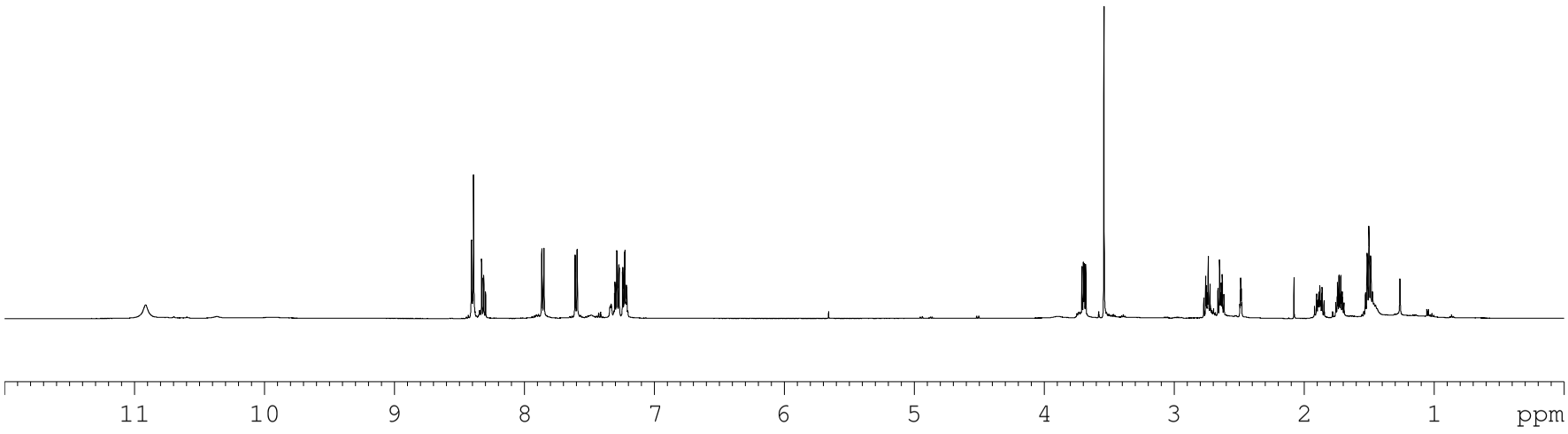
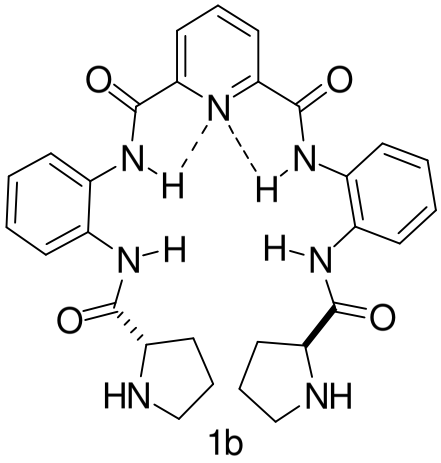


1b

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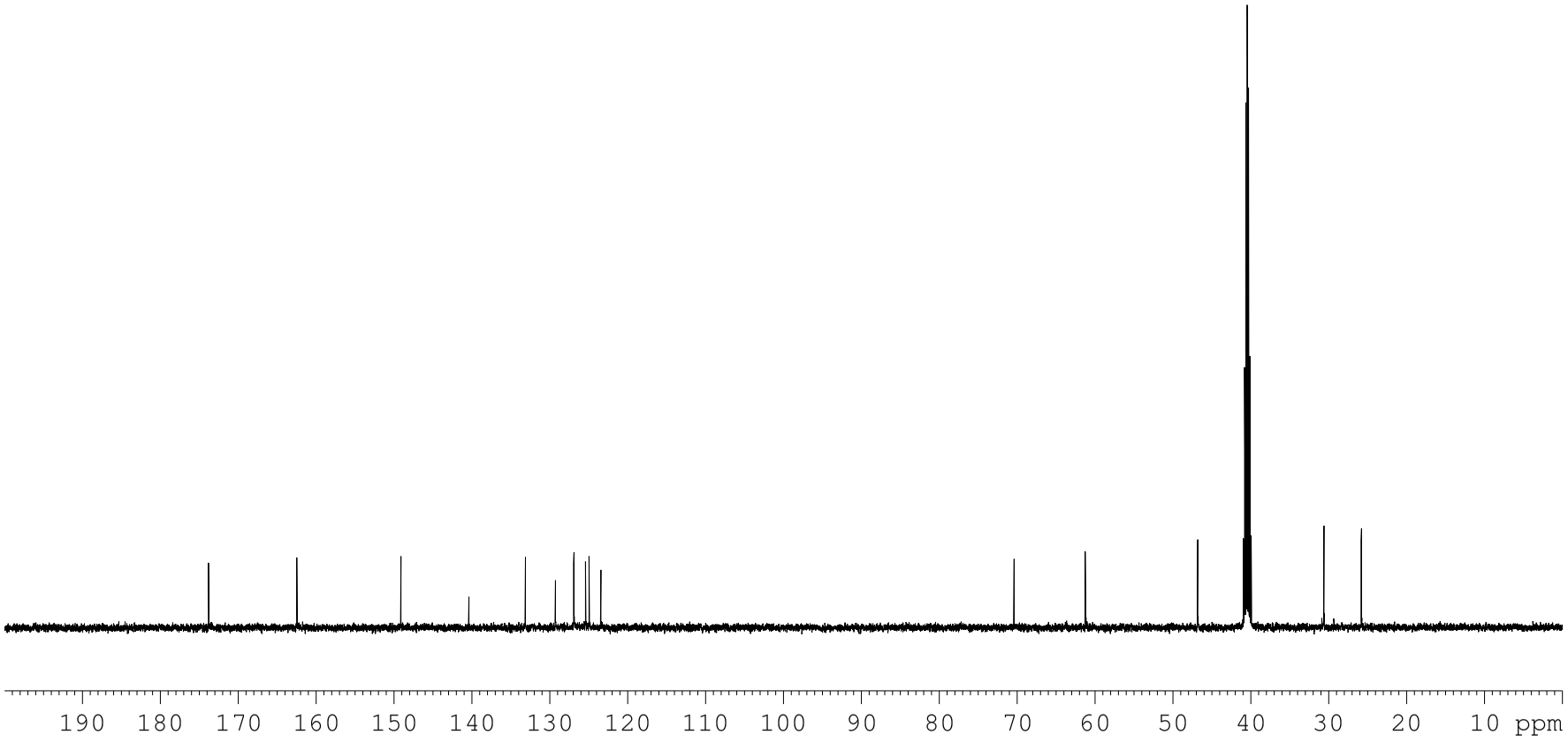
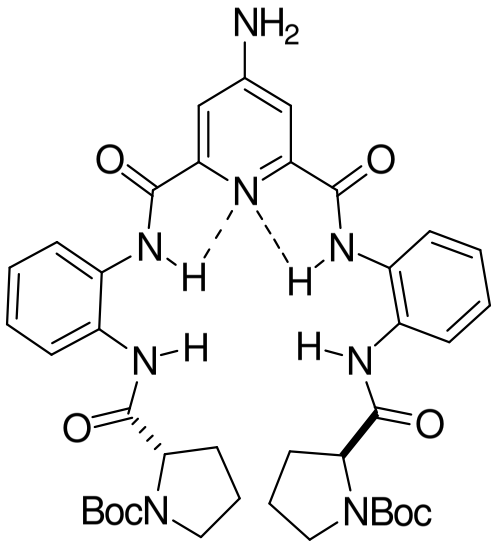
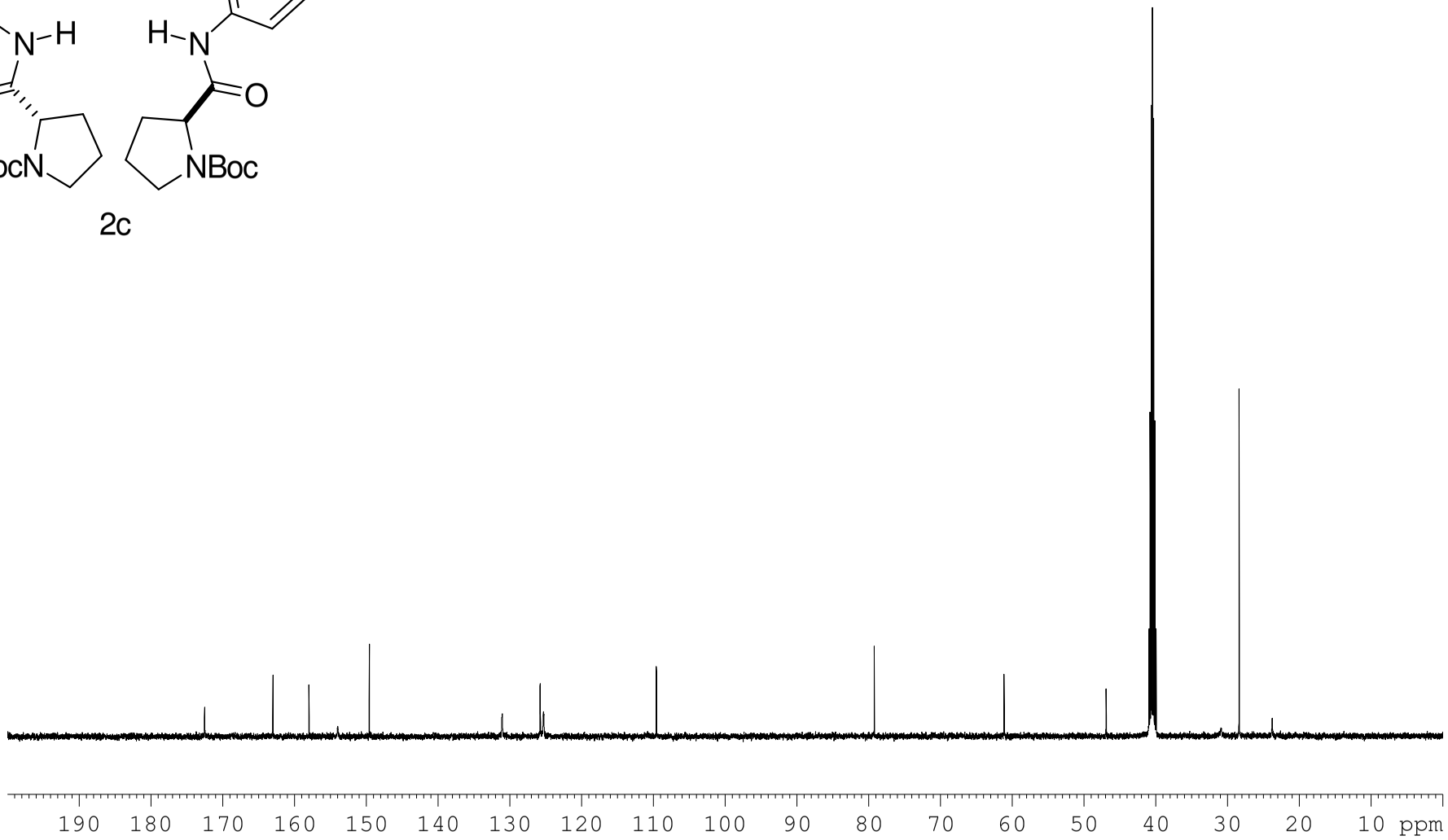
H
N
N
H
H
N
O
O
HN
NH

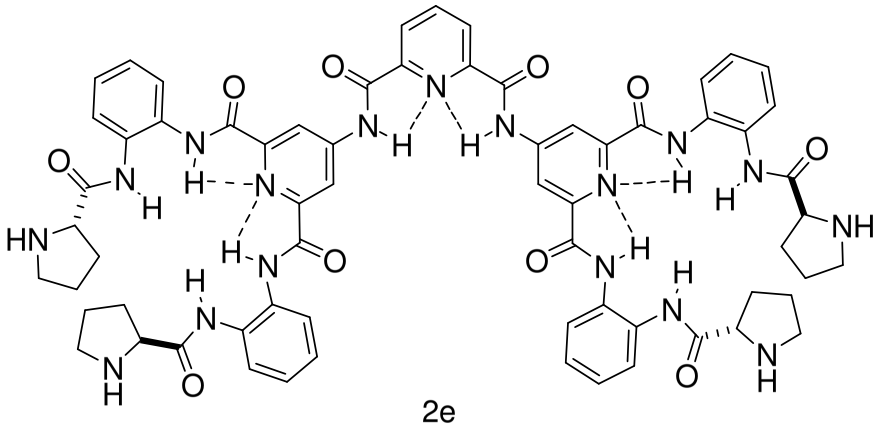
1b


190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

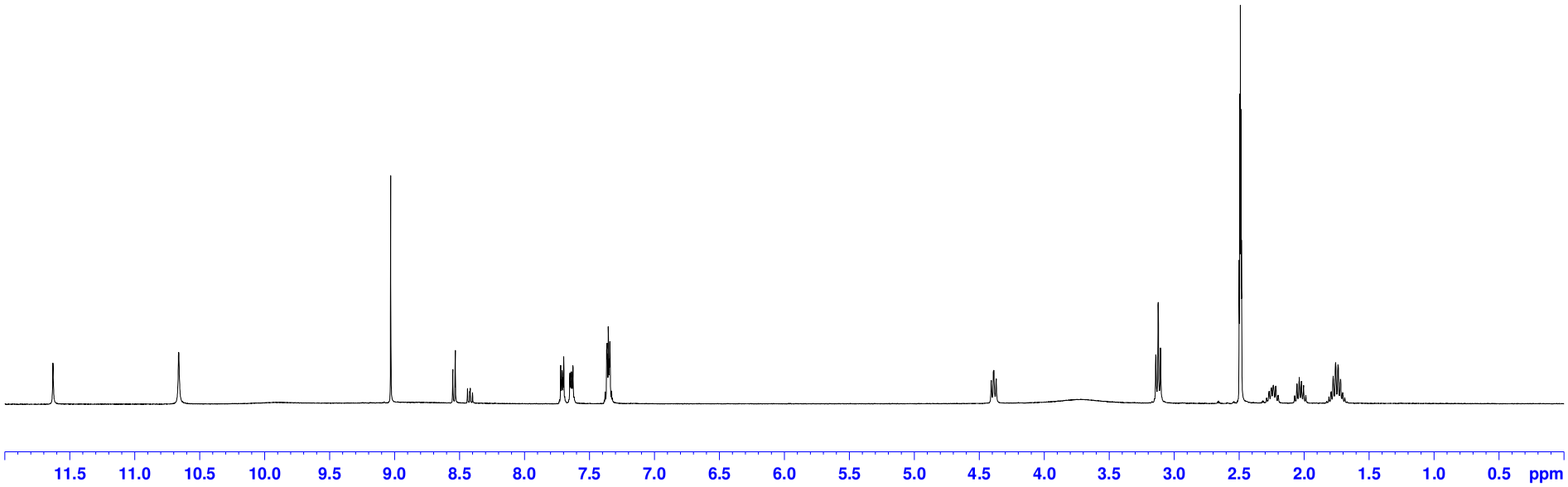

NH2
O
O
N
N
H
H
N
N
H
H
N
O
O
BocN
NBoc

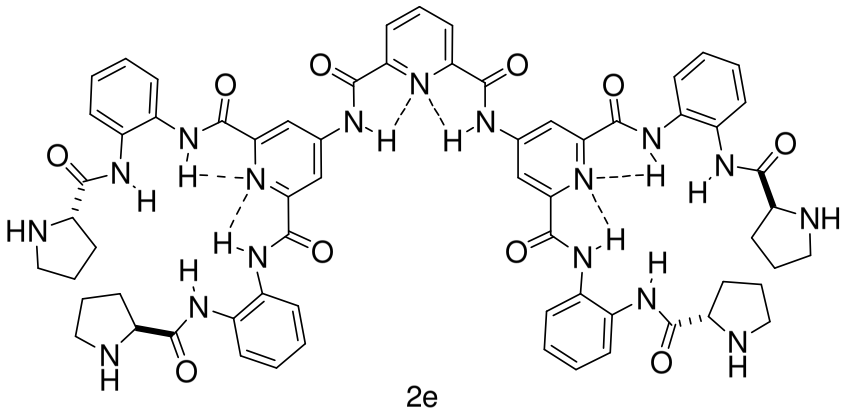
2c


190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm



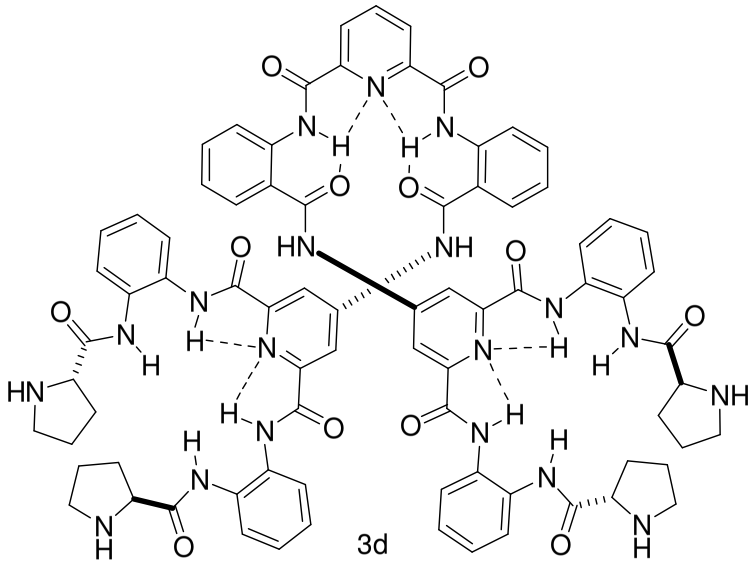
2e

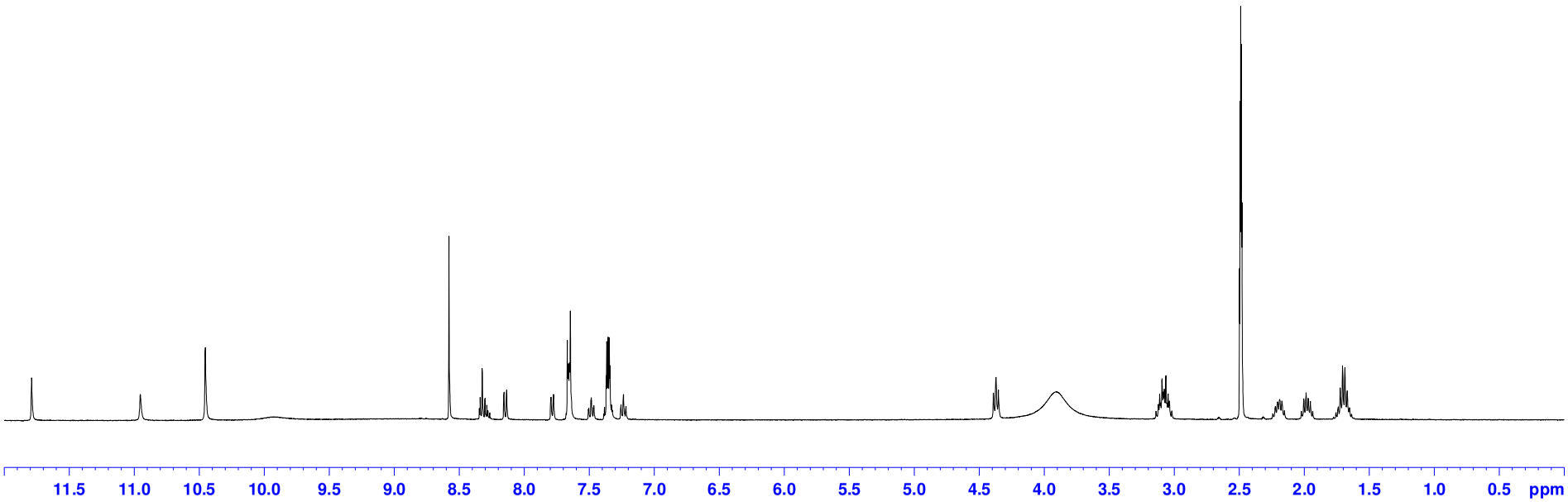

11.5
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

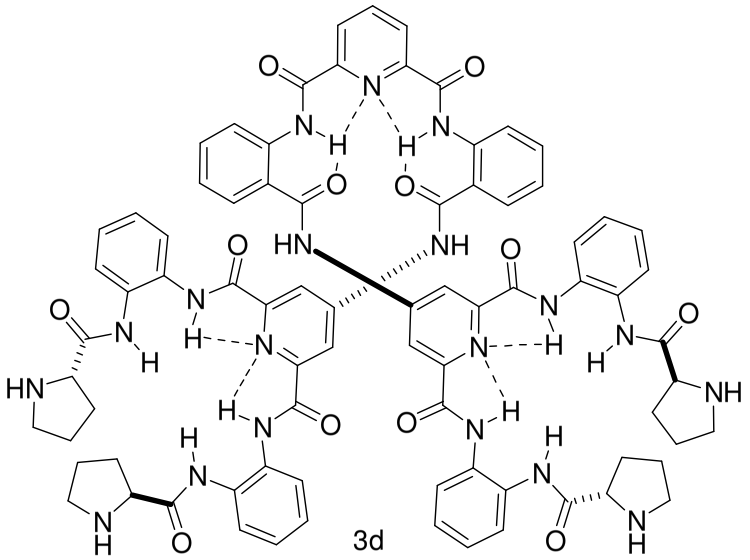


2e

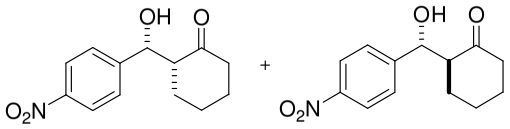
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

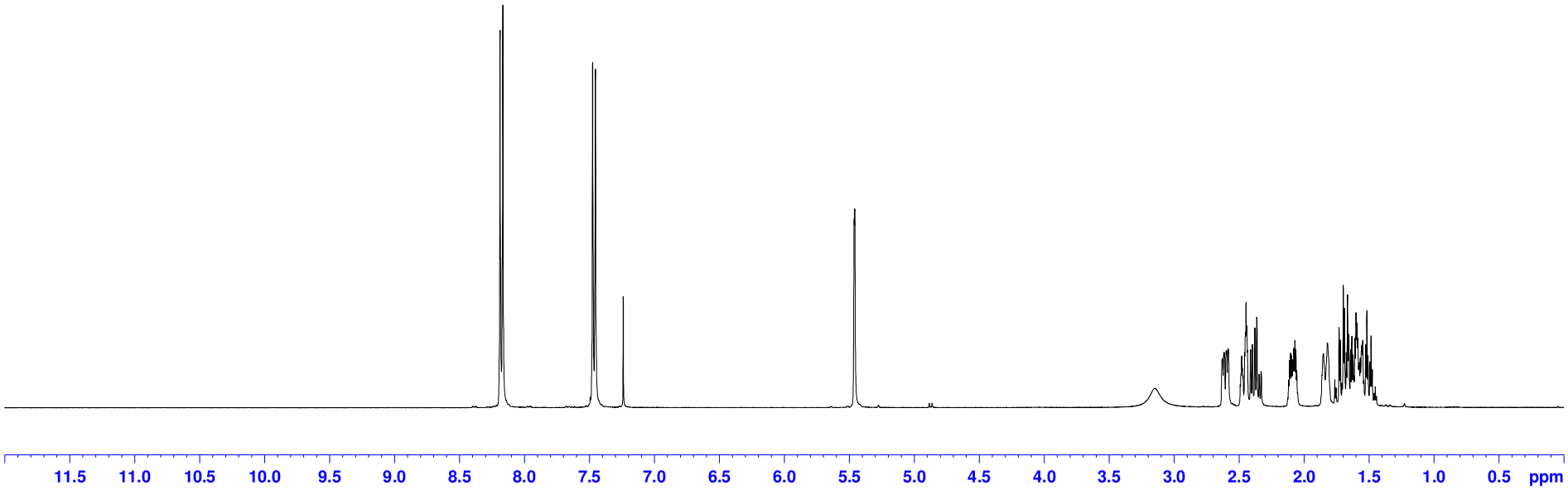

3d


11.5
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm


3d

190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm


OH
O
O_2N
+
OH
O
O_2N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11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
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5.5
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4.5
4.0
3.5
3.0
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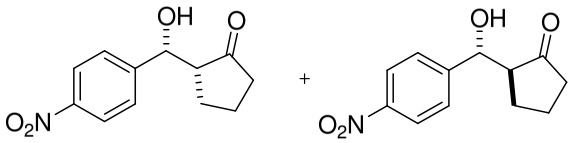
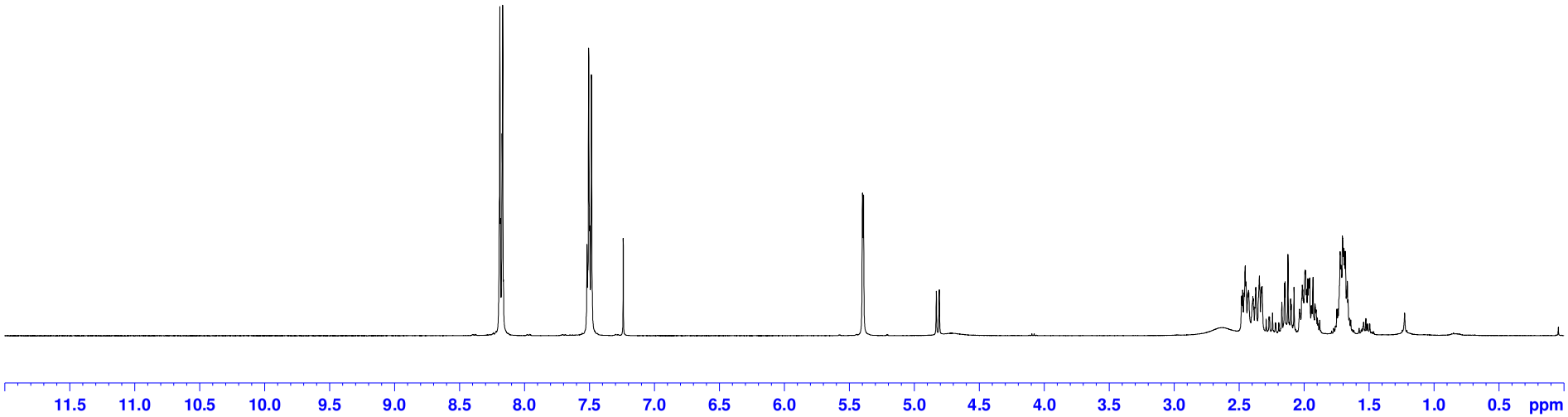
2.0
1.5
1.0
0.5
ppm


OH
O
O2N
+
OH
O
O2N


11.5
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm